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The Adequacy and Uniformity of Federal Rules and of their Implementation

President's Commission for the Study of
Ethical Problems in Medicine and
Biomedical and Behavioral Research

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Implementing Human Research Regulations

Second Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subjects

March 1983

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

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President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

March 30, 1983

The President
The White House
Washington, D.C. 20500

Dear Mr. President:

On behalf of the President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research, I am pleased to transmit our second "Biennial Report" on Implementing Human Research Regulations. The Commission is directed by Public Law 95-622 to report every two years on the adequacy and uniformity of the federal rules and policies for the protection of human subjects in biomedical and behavioral research, as well as the adequacy and uniformity of their implementation. As you will recall, we submitted our first "Biennial Report," Protecting Human Subjects, in December 1981. This report is being submitted 15 rather than 24 months after the first because of the Commission's scheduled termination on March 31, 1983.

In this report, the Commission first reviews the administrative response to recommendations contained in our 1981 report, and finds that most of the recommendations have yet to be implemented. We urge those having oversight of the affected agencies to monitor their progress in this regard after the Commission ceases to exist. We also recommend the reinstitution of an Ethics Advisory Board (EAB) within the Department of Health and Human Services (HHS) to provide guidance on ethical issues as they arise, in line with existing HHS regulations. An EAB could also study several important ethical issues in biomedical and behavioral research that we have identified but have not had an opportunity to resolve.

In the second part of this Report, the Commission addresses the problem of assuring adequate oversight of the process by which Federally supported research involving human subjects is conducted. We have concluded that improvements are needed in this area and recommend that a program of routine site visits to Institutional Review Boards (IRB) be implemented by relevant Federal agencies on a coordinated basis to avoid burdensome duplication. These visits, conducted by knowledgeable peers (IRB members and former members from other institutions) and Federal officials, would serve an educational as well as an administrative function. In addition, we recommend that those agencies that do not already do so identify and keep a record of the IRBs subject to their jurisdiction. The thrust of our recommendations is not to add new regulations but to increase the adequacy and uniformity of the implementation of existing regulations in the interest of public accountability and administrative efficiency.

We appreciate the opportunity to provide suggestions for improving the Federal role in biomedical and behavioral research. Copies of this report are being sent to all affected Federal agencies, with a request for action as appropriate, pursuant to the Commission's enabling legislation.

Respectfully,

Morris B. Abram
Chairman

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

March 30, 1983

The Honorable George Bush
President
United States Senate
Washington, D.C. 20510

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March 30, 1983

The Honorable Thomas P. O'Neill, Jr.
Speaker
U. S. House of Representatives
Washington, D.C. 20515

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Morris B. Abram
Chairman

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Summary and Conclusions

When people rely on rules to protect them from harm, they are not interested in pieces of paper but in the conduct of the people who are supposed to be governed by the rules. Having looked for the most part at the adequacy of the rules in its First Biennial Report on the protection of human subjects in research, the Commission turns in this second report primarily to the question of the rules' implementation.[1]

Part One of this Report reviews the responses of Federal agencies and others to the recommendations contained in the Commission's 1981 report and summarizes the Commission's activities relating to the protection of human subjects during 1982. In Chapter One, the Commission notes some progress by Federal agencies but concludes that overall the response to its

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[1] This division is suggested in § 1802 (c) of the Commission's authorizing statute, which directs that

> The Commission shall biennially report to the President, the Congress, and appropriate Federal agencies on the protection of human subjects of biomedical and behavioral research. Each such report shall include a review of the adequacy and uniformity (1) of the rules, policies, guidelines, and regulations of all Federal agencices regarding the protection of human subjects of biomedical and behavioral research which such agencies conduct or support, and (2) of the implementation of such rules, policies, guidelines and regulations by such agencies, and may include such recommendations for legislation and administrative action as the Commission deems appropriate.

42 U.S.C. § 300v-1(c) (1981). The First Biennial Report, PROTECTING HUMAN SUBJECTS, was issued in December 1981. The Commission's Second Biennial Report is being submitted 15 months (instead of 24) after the first because of the scheduled termination of the Commission in March 1983.

previous recommendations has been disappointing. Since the Commission is now going out of existence, it must leave to appropriate Congressional committees the task of monitoring the Federal agencies' responses to the recommendations in both the 1981 report and this one—and of prodding, if necessary, to stimulate administrative action. In Chapter Two, the Commission identifies a number of issues relating to biomedical and behavioral research that it believes are worthy of further consideration but that it has had neither the time nor resources to address. The Commission hopes that the Department of Health and Human Services will reestablish its Ethics Advisory Board to study these issues as well as to provide consultation and advice to HHS on research proposals presenting unusual ethical problems.

Part Two of this Report explores mechanisms for evaluating the performance of the Institutional Review Boards (IRBs) on which governmental policy for protecting human subjects so heavily relies. In Chapter Three, the Commission describes the shortcomings of current mechanisms used by Federal agencies to monitor IRB performance and to assess the adequacy of their implementation of the rules to protect human research subjects. Because it appears that there is currently no completely satisfactory set of procedures for evaluating the performance of IRBs, the Commission undertook a pilot study to determine whether a program of site visits, using IRB members and administrators as site visitors, would prove a useful mechanism for assessing the extent to which IRBs meet the intent of the Federal regulations and also to assist them in identifying—and correcting—their shortcomings.

Chapter Four describes and discusses the results of the IRB site visit project. Specifically, it was learned that peer-based site visits can be a valuable approach for identifying procedural problems that may interfere with the functioning of an IRB but that are not necessarily apparent from a review of the institution's general assurance of compliance with HHS regulations or from the minutes of IRB meetings. Attendance at these meetings proved to be an important part of the IRB site visits. It was also learned that there is great diversity in the way IRBs interprete and implement the regulations—in part, because the intent of the regulations is not always entirely clear.

In Chapter Five, the Commission reviews several possible approaches to monitoring the performance of IRBs, including FDA inspections, private accreditation programs, and site visits of the kind performed in the pilot study. The Commission concludes that peer-based site visits could become a part of a Federal educational and monitoring program without unduly straining the administrative budget.

Part Three of the Report contains the Commission recommendations to the President, the Congress, and the Administrative agencies that conduct or support biomedical and behavioral research. Based upon its findings and conclusions, the Commission makes six recommendations, which can be summarized as follows.

Improving the Adequacy of the Regulations:

(1) Congress should monitor the progress of administrative agencies in responding to the Commission's recommendations.

(2) HHS should reestablish an Ethics Advisory Board.

(3) The meaning of certain regulatory requirements should be clarified.

Improving Implementation of the Regulations:

(4) There should be a uniform Federal system documenting the implementation of the regulations through prior assurances and periodic site visits.

(5) An assurance process should provide prior assurance of the adequacy of each IRB's composition, procedures, and institutional support.

(6) A program of site visits to IRBs should be established as part of agencies' educational and monitoring efforts.

Improving the Regulation of Research with Human Subjects

I

Responses to the First Biennial Report

1

The Commission made nine recommendations in its First Biennial Report on human research regulations, *Protecting Human Subjects*, in 1981.[1] Six recommendations were designed to improve the adequacy and uniformity of the regulations governing Federally supported research with human subjects; three recommendations were designed to improve implementation of those regulations. In this chapter, the Commission reviews the response to the recommendations of *Protecting Human Subjects:*

- **Recommendations for improving the adequacy and uniformity of Federal laws and regulations for the protection of human subjects**

(1) All Federal agencies should adopt the regulations of HHS (45 CFR 46).

(2) The Secretary, HHS, should establish an office to coordinate and monitor government-wide implementation of the regulations.

(3) Each Federal agency should apply one set of rules consistently to all its subunits and funding mechanisms.

(4) Principal investigators should be required to submit annual data on the number of subjects in their research and the number and nature of adverse effects.

(5) The National Commission's recommendations on research involving children and the mentally disabled should be acted upon promptly.

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[1] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, PROTECTING HUMAN SUBJECTS, U.S. Government Printing Office, Washington (1981).

(6) "Private" research organizations receiving direct Congressional appropriations should be required to follow Federal regulations for the protection of human subjects.

- **Recommendations for improving institutional and Federal oversight of research and the response to reports of misconduct**

(7) Institutions should be free to use offices other than IRBs to respond to reports of misconduct and should have procedures for prompt reporting of their findings to the funding agency.

(8) IRBs should be required only to report to appropriate officials of their institution (rather than to the funding agency) when they learn of possible misconduct and to respond to the findings of those officials.

(9) There should be government-wide procedures for debarring grantees and contractors found guilty of serious misconduct, as well as a consolidated list of formal debarments and suspensions actively shared with government agencies, professional societies, and licensing boards.[2]

Establishing Uniform Rules

The Commission's 1981 examination of the regulations of 22 Federal departments and agencies supporting research with human subjects revealed that virtually all agencies follow the policies and procedures of the Department of Health and Human Services (HHS) to some extent.[3] There were sufficient variations, however, to make it difficult for local institutional review boards (IRBs) to comply with the different sets of regulations—especially since at the time an IRB reviews a proposal it is not always clear which agency will be funding the research.[4] The Commission determined that IRBs would find it easier to fulfill their responsibilities for assuring the ethical acceptability of research projects if they had to apply only one set of rules.

Recommendation (1) was that all Federal agencies adopt HHS rules (codified at 45 CFR 46) as a central core.[5] This

[2] *Id.* at 67-83.

[3] *Id.* at 28.

[4] *Id.* at 28-32; *see also* Appendix C, *id.* at 109.

[5] Recommendations (1) and (3) were alternative recommendations. The text discusses only Recommendation (1), the preferred alternative, which would provide a uniform set of regulations throughout the Federal government. Recommendation (3) was that if the first recommendation were not implemented, then each department should at least have one set of regulations applicable to all departmental research with human subjects, whatever the mechanism of support (*e.g.*, grant or contract) and whatever part of the department was involved. Clearly, if the first recommendation were adopted, the third would be unnecessary.

recommendation has met with almost universal approval from Federal agencies as well as from scientists and research institutions. Early in 1982, the President's Science Advisor, Dr. George Keyworth, named an interagency Ad Hoc Committee on Protection of Human Subjects to develop a coordinated response to the Commission's recommendations. The Committee, chaired by HHS Assistant Secretary for Health, Dr. Edward M. Brandt, Jr., was established under the aegis of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), and it included representatives of all agencies and departments that support or conduct research with human subjects. Ex officio members included representatives of the Office of Science and Technology Policy, the Office of Management and Budget, the Department of State, and the President's Commission. (The charter and a list of members of the Committee appears in Appendix A.)

It was initially expected that the Ad Hoc Committee would publish a set of guidelines, endorsed by all affected agencies, in the Federal Register by the end of 1982. However, the process of developing policies was more difficult than anticipated; thus, no unified set of regulations governing all Federal agencies that conduct or support research with human subjects is yet in place. The Commission has been informed that this will be achieved sometime in 1983.

Recommendation (2) of the Commission's 1981 Report was that the Secretary of HHS should establish an office to coordinate and monitor the government-wide implementation of the uniform set of regulations. At meetings of the Ad Hoc Committee on Protecting Human Subjects, discussed above, HHS Assistant Secretary for Health Brandt indicated the Department's intention to designate the National Institutes of Health's Office for Protection from Research Risks (OPRR) as the responsible office. It appears, however, that neither HHS nor the other agencies intend OPRR to have authority to monitor the actual implementation of the rules, or even to make decisions regarding acceptable modifications of the "core" regulations. Rather, the proposed role of OPRR is apparently an advisory one.

The Commission's suggestion that the coordinating office be established in the Office of the HHS Secretary was based upon the premise that the office would have authority to approve or disapprove deviations from, or amendments to, the core regulations. The Commission believed that only a unit within the Office of the Secretary would have sufficient stature to exercise such authority over other agencies. If the office is not to have such authority, its placement within the HHS bureaucracy is of less concern. Since no formal proposal regarding the designation of OPRR as the coordinating office

has yet been issued, the Commission is unable to comment on the possible allocation of duties and authority.

Improving Oversight of Research with Human Subjects

As part of its investigation of the adequacy of the implementation of the rules governing research with human subjects, as discussed in the 1981 Report, the Commission reviewed several widely reported cases of alleged misconduct by scientists whose research was supported by HHS grants or contracts.[6] Based upon its own inquiry, an examination of current monitoring procedures, and the several cases examined, the Commission concluded that certain weaknesses exist within the HHS system for protecting human subjects, primarily: (1) inadequate understanding of the Federal requirements on the part of research investigators and IRBs, and (2) insufficient oversight of investigators and IRBs on the part of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).[7]

NCI-FDA Task Force on Investigation of New Drugs. Many of the problems identified by the Commission in its First Biennial Report were presented by the Commission's Executive Director and Deputy Director during Congressional hearings on the National Cancer Institute (NCI) and its research programs.[8] As emphasized at that time, the need for improvement was not limited to research sponsored by NCI; rather, the Commission believed the entire HHS system of oversight needed strengthening.

In response to the criticisms (by the Commission and others) aired at those hearings, HHS Assistant Secretary Brandt established an NCI-FDA Task Force in the Fall of 1981 to examine NCI's program for the development of new chemotherapies and the oversight of such research by both FDA and NIH. The Task Force, composed of HHS officials and

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[6] PROTECTING HUMAN SUBJECTS, *supra* note 1, at 53-60; *see also* Appendix F, *id.* at 177.

[7] *Id.* at 35-60.

[8] 4 *Fraud in Biomedical Research*, Hearings before Subcomm. on Investigations and Oversight Comm. on Science and Technology, U.S. House of Representatives (March 31-April 1, 1981); *National Cancer Institute's Therapy Program*, Joint Hearing before Subcomm. on Health and the Environment, Comm. on Energy and Commerce, and Subcomm. on Investigations and Oversight, Comm. on Science and Technology, U.S. House of Representatives (Oct. 27, 1981); and *Oversight of the National Cancer Institute: Examination of Deficiencies in the Use of Experimental Drugs on Cancer Patients*, Hearings before Subcomm. on Investigations and General Oversight, Comm. on Labor and Human Resources, U.S. Senate (Nov. 3 and 6, 1981).

scientists, was asked to: (1) assess NCI procedures for monitoring INDs (Investigational New Drug applications); (2) assess FDA's review of NCI activities relating to the development of new drugs; and (3) develop recommendations for improvement.[9] Included in the review of the Task Force were problems regarding the actual performance of IRBs, agency monitoring of the IRBs, and overall compliance with regulations governing research with human subjects—particularly requirements for informed consent.

The Task Force solicited testimony from the Commission's Executive and Deputy Directors along with others who had been critical of various aspects of the NCI program for developing new anti-cancer drugs. As the Commission had done, the NCI-FDA Task Force reviewed several cases "to elucidate concerns about reported lack of accountability; gaps in communication; ambiguity about roles and responsibilities of institutions, institutional review boards (IRBs), NCI investigators, and FDA staff; therapeutic intent; and sanctions."[10] After a thorough review of voluminous materials, the Task Force made the following findings.

- Regarding Informed Consent:

The cancer patient faces extremely difficult treatment decisions in traditional and research situations. It is crucial, therefore, that patient decisions be made on the basis of complete and frank information. In Phase I trials, for example, the physician disclosing information to the potential research participant must be particularly careful to describe fully "reasonably forseeable risks and discomforts," "any benefits to the subject or others which may reasonably be expected," and to include a statement that "participating is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled." (HHS 45 CFR 46.116) The Task Force concurs that information disclosed for Phase I must include a statement about the small possibility of direct benefit to the patient him/herself.

The informed consent form and process should reflect the different proportions of risks and benefits anticipated as the investigational new drug passes from the first use in human subjects in Phase I through Phase II, III, and beyond. Some Task Force members felt that the patient should also be told how many subjects had

[9] Task Force on NCI-FDA Investigational New Drugs, 2 REPORT ON ANTICANCER DRUGS: THE NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION, U.S. Dept. of Health and Human Services, Washington (1982) at 2 (hereinafter cited as NCI-FDA TASK FORCE REPORT).

[10] *Id.* at 13-14.

preceded him/her in the protocol and what the results were.[11]

- Regarding the performance of IRBs:

Problems continue to plague the IRBs and their performance. A specific example was the findings of an investigation by FDA on March 20, 1982, of the IRB at the M.D. Anderson Hospital and Tumor Institute. That evaluation revealed some commonly encountered problems. The M.D. Anderson IRB procedures for annual review of clinical investigations were found inadequate in that review of the project level did not ensure that each study had been reviewed. The IRB was not informed when a study had been terminated, and most importantly, information on ADRs [adverse drug reactions] and patient population and protocol changes were never brought to the IRB's attention.

There is general agreement within the Task Force that the IRB, in principle, represents a critical force in ensuring the protection of human subjects in cancer investigations and other aspects of patient health care interaction. There is reason to believe, however, that the experience of IRBs has been marked by numerous problems, failures, and inconsistencies. Part of this is directly related to the absence of specific direction and education of members.[12]

- Regarding NCI Review and Oversight:

Reviewers at each level approach the [consent] form globally (*i.e.*, no one is assigned a particular aspect to review), utilizing their knowledge of the drug and their experience as investigators. None of the NCI review levels uses the elements of informed consent delineated in 45 CFR 46 in a systematic way to perform the review.

NCI does not routinely coordinate with OPRR regarding issues of informed consent, although it occasionally consults with that office about special situations.[13]

- Regarding Oversight by the NIH Office for Protection from Research Risks (OPRR):

OPRR screens summary statements on research projects prepared by NIH initial review groups (approximately 10,000 grants per year deal with human subjects research) for compliance with 45 CFR 46.

The contracts and cooperative agreements reviewed in NCI committees provide the primary funding support for the NCI-sponsored investigational new drug studies. The Task Force is concerned that OPRR may not routinely

[11] *Id.* at 73.
[12] *Id.* at 76.
[13] *Id.* at 78.

receive summaries prepared for scientific merit review of contract proposals and grant and cooperative agreement applications assigned to NCI-based public advisory committees. Thus, OPRR review of human subjects protection in research may exclude most of the NCI-sponsored cytotoxic drug research program.[14]

Based upon those findings, the NCI-FDA Task Force made the following recommendations.

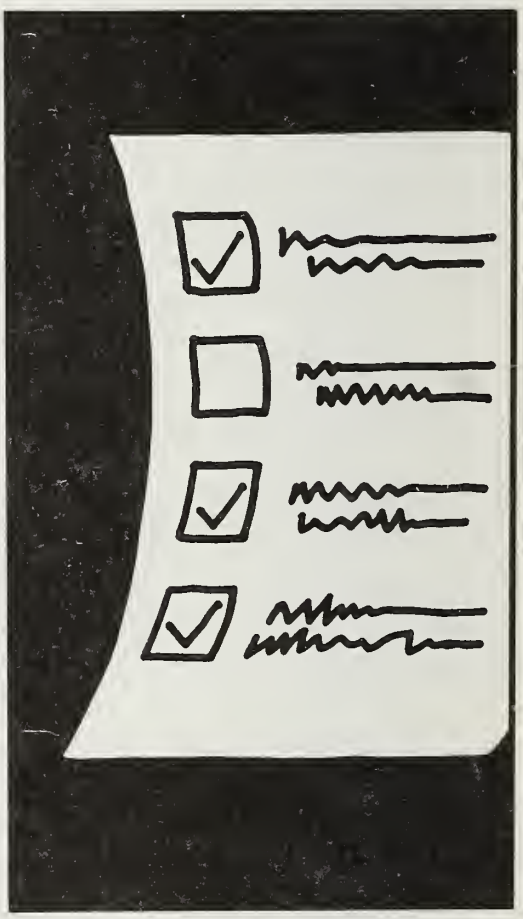
Additional steps should be taken to improve compliance with existing FDA and HHS regulations. They are as follows:

- NCI and FDA reviewers of informed consent forms should become more familiar with the required elements of the FDA and HHS regulations and use a reference review guide that lists the required elements of the regulations to ensure that the consent forms are thorough and specific and are evaluated against the requirements.
- Feedback from NCI and FDA review of informed consent forms should be made to IRBs and to investigators; FDA Bioresearch Monitoring inspections should categorize deficiencies in informed consent forms from site visits so that summary data can be compiled for educational activities and to provide needed feedback.
- IRBs should encourage lay members to review consent forms to determine that language is understandable and not unnecessarily technical, and encourage all members to use a review guide for review of informed consent forms.
- OPRR should develop an educational program for all participants in the consent process—sponsors, institutional representatives, and investigators—to spell out their respective responsibilities and methods to ensure maximum communication of the risks and benefits of participation in clinical trials.
- OPRR should—(a) proceed to select at random and review consent forms approved by IRBs; (b) expand the current review of grant summary statements for protection of human subjects to include NCI contracts; and (c) initiate reviews of investigators, IRBs, and institutions to determine adherence to regulations.
- NCI should increase its operational ties with OPRR with regard to protection of the rights of cancer patients.[15]

[14] *Id.*
[15] *Id.* at 80-81.

In summary, the NCI-FDA Task Force identified the same deficiencies in the IRB system as the Commission had; indeed, the Task Force was in many respects more critical than the Commission and more specific regarding recommendations for improvement.

Current Status of OPRR's Efforts to Improve Oversight of IRBs



Education. OPRR began planning an education program in 1979, in response to the mandate of the National Research Act (PL 93-348) and the recommendation of the National Commission for the Protection of Human Subjects.[16] The plan was to initiate the education program in conjunction with the FDA after publication of final revised regulations. Completion of the development phase had to await publication of final regulations in January 1981.

The education program currently includes development of: written explanatory materials; educational activities (workshops, conferences, seminars); "autotutorial" materials (*e.g.*, videotapes, audio cassettes, self-study guides); and training programs. Development of written materials has been coordinated with FDA and the President's Commission in the IRB Guidebook.

Workshops sponsored by OPRR and FDA for Federal officials, IRB members, institutional officials and researchers have been held throughout the country. NIH and FDA personnel also participate in regional and national meetings sponsored by nongovernmental organizations. Since Spring of 1981, OPRR and FDA have co-sponsored 23 workshops: 10 for Public Health Service staff (including NIH, FDA, ADAMHA, and CDC); 4 for IRBs associated with Federal agencies; and 9 for the extramural research community. Another 12 workshops for the extramural research community are planned for FY 1983.

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[16] Information in these two sections was provided in a letter from Charles R. McCarthy, Director, OPRR, to Barbara Mishkin, and the attached *Response to August 11 Request for Information from the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research* (Sept. 2, 1982).

Additional workshops for Federal employees will also be held, and plans are under consideration to establish a training program for Federal agency personnel who are responsible for protecting human subjects.

Direct costs associated with the education program (excluding staff time and travel) have been $340,000 for the period from June 1980 through September 1982. The FDA contributed $80,000 of that amount. OPRR reports that participation in its workshops was as follows:

10	Public Health Service Staff workshops	210
4	Workshops for Federal officials and IRB members	450
9	Regional Workshops for Extramural Community	1000

Both NIH and FDA however, consider the workshops too "resource-intensive" in terms of staff time to provide a long-range response to the educational needs of the research community. Thus, primary emphasis is now being directed toward the development and distribution of educational materials such as videotapes, audio cassettes, and interactive computer programs. An evaluation of the program is planned for FY 1983.

Compliance activities. The 1981 amendments to the HHS regulations for the protection of human subjects required certain changes in assurance documents, including a greater degree of specificity. As a consequence, all institutions having a General Assurance with HHS were alerted that revised assurances must be submitted by December 31, 1982. As an aid in developing the new assurances, OPRR distributed a "model" with the letters notifying institutions of the need to submit a new assurance. OPRR believes that institutions are now more keenly aware of their responsibilities to human subjects and their accountability to HHS as a result of going through the process of developing a new assurance.

As described more fully in Chapter Three of this Report, the Public Health Service has instituted procedures whereby scientific review groups, agency staff, and national advisory councils also review applications for PHS grants and contracts to assure that human subjects will be adequately protected. This review provides some oversight and additional feedback to IRBs regarding their performance.

Developing Policies and Procedures for Responding to Reports of Misconduct

After examining the response of both research institutions and the NIH to reports of misconduct in the six cases reviewed in 1981, the Commission concluded that improvement was needed at both levels. Recommendations (7) and (8) in the First Biennial Report were designed to assure flexibility for the institutions in fashioning their mode of response while encouraging them to establish formal policies and procedures as part

of their formal assurance to HHS that they will fulfill their responsibilities under the regulations governing research with human subjects. Recommendation (9) was designed to improve the response at the agency level by assuring that formal policies and procedures are in place for a timely and fair response to reports received at any office within HHS.

Based upon its own review of cases and the recommendations developed at the Workshop on Whistleblowing in Biomedical Research (cosponsored with Medicine in the Public Interest and the Committee on Scientific Freedom and Responsibility of the American Association for the Advancement of Science),[17] the Commission expressed concern that all parties involved in a report of misconduct be protected: the accused investigator(s), the complainant(s), any human subjects involved in the research, the research institution, and other members of the research team who might be affected by the imposition of sanctions. The Commission encouraged research institutions, professional societies, and Federal agencies to show their commitment to maintaining the highest standards in Federally funded research by: (1) establishing clear norms and guidelines; (2) taking reports of problems seriously; (3) acting fairly and promptly to resolve complaints; (4) imposing appropriate sanctions when serious misconduct has occurred; and (5) providing guidance through education and example. Response to these recommendations has for the most part been good.

HHS Clarification of Departmental Policies. During the Commission's first year, as it reviewed cases in which violation of human subjects' rights had been alleged, the Commissioners became concerned that the policies and procedures of the Department of Health and Human Services did not provide clear guidance to the people charged with their implementation either at research institutions or within HHS. The Chairman of the Commission first wrote to Secretary Patricia Harris on September 18, 1980, asking for clarification of the applicable standards.[18] In April 1981, Secretary Richard Schweiker replied that, in effect, there were no substantive or procedural standards and that each case would be decided according to the circumstances. Not satisfied with this response, the Commission requested a meeting with the Secretary, HHS.

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[17] Judith P. Swazey and Stephen R. Scher, eds., WHISTLEBLOWING IN BIOMEDICAL RESEARCH, U.S. Government Printing Office, Washington (1982).

[18] The First Biennial Report documents the lengthy and inconclusive exchange between the Commission and HHS concerning Departmental policies for responding to reports of misconduct. See PROTECTING HUMAN SUBJECTS, Chapter 3 and Appendix F.

The meeting between the Secretary and the Assistant Secretaries for Health and for Policy and Planning, and the Commission's chairman, executive director, and deputy director occurred on December 3, 1981. At its conclusion, the Secretary asked the Assistant Secretary for Planning and Evaluation to respond on behalf of the Department to the questions posed by the Commission. The Commission was assured that explicit guidelines for handling alleged misconduct would be developed promptly, taking into account the Commission's concerns about the rights of the accused, complainants, and others on the research team, as well as the interests of human subjects, the research institution, and the general public.

Fourteen months later, the Assistant Secretary for Planning and Evaluation wrote to the Commission, suggesting that the Department had made "significant progress" [*see* Appendix B]. Although the roles of the several components of HHS in responding to problems with human research have been more fully explained, in essence the Department continues to adhere to an ad hoc method of decisionmaking. Moreover, the relationship between "material failure" to protect subjects and formal debarment proceedings remains inchoate.

> Although use of the term "materially failed" leaves room for administrative discretion, it was intentionally chosen to require an affirmative finding of seriousness-in-fact before early termination of research funding may be initiated....While the phrase insures exclusion of, for example, trivial procedural failures, it gives the Department sufficient latitude to consider a full variety of serious offenses, including such violations or offenses and the circumstances surrounding them that cannot be fully anticipated in advance.

In response to the Commission's question concerning the standards governing decisions to initiate proceedings for debarment or suspension, the Department stated:

> [D]ebarment is intended as a sanction appropriate only in the most serious cases of fraud and abuse by grantees or recipients of other forms of financial assistance. The Department recognized at the time of publication that the rule allows substantial administrative discretion.
>
> [F]inal authority to suspend or debar for human subjects' infractions under 45 CFR 46 is reserved exclusively to the Secretary. In exercising that authority, the Secretary will consider elements such as the degree and intentionality of risk, the gravity of harm to human subjects, and prior offenses against human subjects' and other regulations.

The Department termed as "largely theoretical" an investigator's or sponsoring institution's use of the debarment proce-

dures as a means of speeding resolution by the Department of allegations brought under 45 CFR 46.

> Finally, it is unlikely that institutions or grantees would wish to request initiation of debarment to invoke its hearing provisions to present additional or mitigating information. The development and investigation processes preceding virtually all sanctions or actions which the Department might take at the agency, OPDIV, and Office of the Secretary levels with regard to 45 CFR 46 or other violations allow for formal and/or informal appeals and/or the consideration of additional information without the applicant having to invoke the debarment provisions.

The Commission had also suggested that it was important for responsibilities to be clearly enunciated, and it had inquired particularly about the roles and authority of the offices at NIH and between NIH and the Office of the Secretary. HHS replied that "lead responsibility" rests with the Office for Protection from Research Risks (OPRR), a component of the Office of the NIH Director, for screening complaints, as for other aspects of human subjects' protection. In executing these responsibilities, "OPRR calls upon other components of NIH and the Department as necessary."

> Findings, conclusions, and recommendations made by OPRR following necessary investigations are subject first to the review of the Associate Director for Extramural Training and Research and, as necessary, through the Associate Director, subsequent reviews by the NIH Director, the Assistant Secretary for Health, and the Secretary. In urgent cases, such additional reviews may be undertaken concurrently. Similarly, as appropriate, other NIH and Department components will have been kept informed of progress during the various stages of OPRR's investigation.

In response to related suggestions made by the Commission in the First Biennial Report, the Department rejected placing the central office that oversees the implementation of the human subjects' regulations within the Secretary's office, where it could better coordinate the activities of all HHS components including NIH, FDA, and ADAMHA.

> There is some theoretical appeal to centralizing responsiblity for receipt of complaints, conduct of investigations, and, where appropriate, imposition of subsequent sanctions in OS [Office of the Secretary]. Such centralization would appear to improve control and accountability. The Department believes, however, that the costs associated with such centralization substantially outweigh these apparent benefits....By reserving to the Secretary and his office a review and approval function,

the Department believes most of the benefits which flow from centralization can be had concurrent with those of decentralization.

NCI-FDA Task Force on Investigation of New Drugs. The NCI-FDA Task Force discussed earlier took a strong stand on the need to impose sanctions in cases of serious misconduct in the performance of Federally regulated research:

> Judicious use of sanctions in appropriate cases serves several important purposes. Not only does it punish the wrongdoer, but it also (1) serves as a reminder to others of the requirements that were transgressed; (2) underscores the importance the agency places on these requirements; and (3) may deter potential wrongdoers.[19]

The Task Force recommended that clear and straightforward violations of NCI or FDA requirements should be met by appropriate action as follows:

(1) NCI should more actively impose sanctions against wrongdoers.

(2) NCI management officials should be reminded of their obligations to report violations of federal rules and regulations to appropriate law enforcement authorities, *e.g.*, HHS Inspector General.

(3) Sanctions should be considered against the institution as well as the individual wrongdoer when multiple violations occur at a single institution, when appropriate.

(4) 45 CFR Part 74 should be amended to allow suspension or termination of a grant, not only for causes related to that grant, but for causes related to activities of the investigator in other contexts.

(5) The Director, NIH, should review the NCI procedures for denying investigators use of NCI-sponsored drugs for clinical investigations to ensure that the procedures are fair and to provide for consistent treatment of investigators.[20] The Task Force made no mention of the process of clarifying the rules on "material failure" then going on within the Department, nor do the Task Force's recommendations seem to have entered into the Department's communication with the Commission or its review of the regulations to protect human subjects. The precise impact of the Task Force's recommendations in this regard remains to be seen.

National Institutes of Health. The NIH Associate Director for Extramural Research and Training, Dr. William F. Raub, established a working group of scientists and administrators to

[19] NCI-FDA Task Force Report, *supra* note 9, at 116.
[20] *Id.* at 17.

refine the agency's procedures for responding to reports of misconduct "to ensure, as far as possible, that NIH actions with respect to instances of real or apparent misconduct will serve to protect the public interest with due regard for the rights of individuals and institutions accused of wrongdoing."[21] The following topics were reviewed by the working group, the NIH Director's Advisory Committee, and the national advisory councils and boards of the various institutes:

- detection of real or apparent problems;
- determination of whether a real problem exists;
- imposition of temporary sanctions or other interim actions prior to completion of an investigation;
- investigation of problems;
- administrative action following completion of an investigation.[22]

The NIH also solicited comments and suggestions from the research community.[23] The policy statement that has been developed is still undergoing review within the Public Health Service and has not been released or distributed for comment.

In Recommendation (9) the Commission suggested that a uniform set of procedures be established for the response of Federal agencies to reports of misconduct. The procedures should be designed to protect the rights of all concerned, taking into consideration such factors as those being studied by the NIH working group. Once those procedures have been invoked in a particular case, if a scientist (with all protections of hearings and legal representation) is found guilty of serious misconduct, that formal finding should be conveyed to other Federal agencies, along with the determinations on which it was based.

The point is that scientists found guilty by one agency of serious abuse of human subjects or other significant misconduct should not receive research support from other agencies without their knowing of the first agency's determination. The recommendation was based upon regulations published in 1981 by the Office of Management and Budget that provide such a uniform standard and consolidated list of debarred individuals for persons receiving Federal *contracts*. In fact, the debarment procedures set forth in those regulations are identical to those of HHS (except that the HHS procedures apply to recipients of *grants* as well).[24] Thus, the Commission did not recommend

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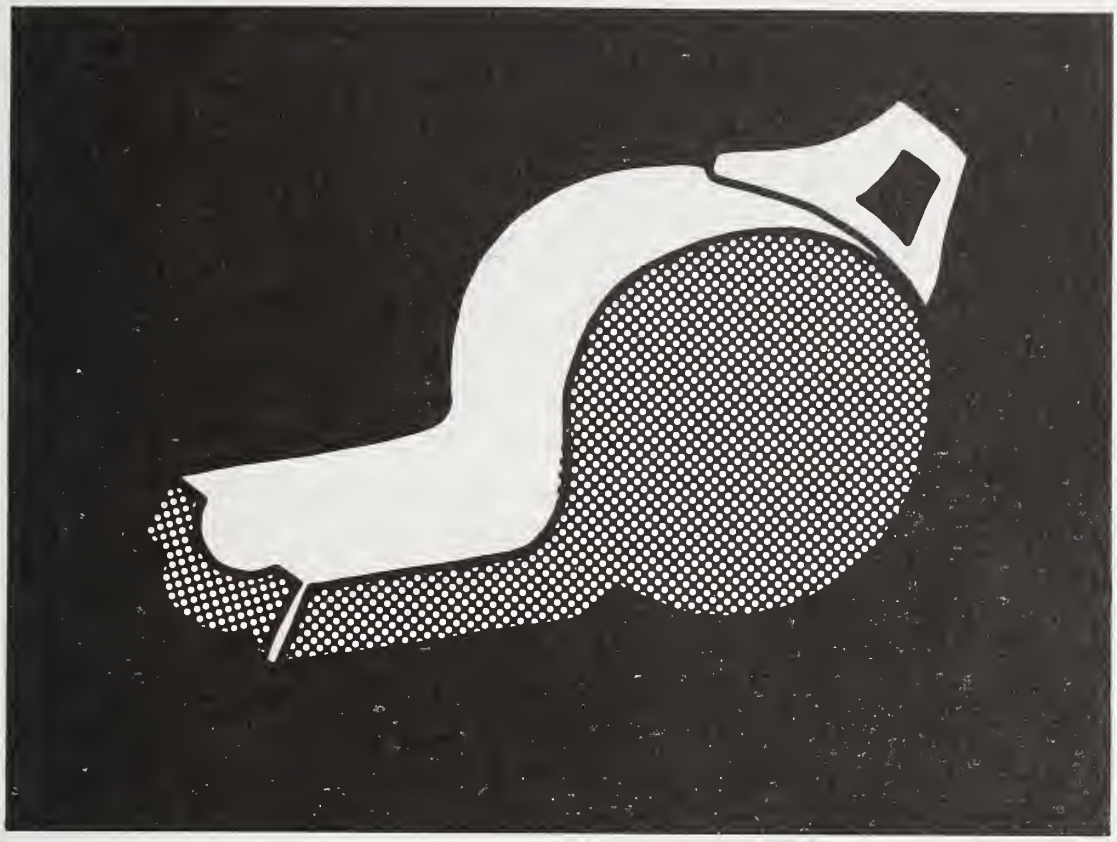
[21] *Notice: Misconduct in Science*, 11 NIH GUIDE FOR GRANTS AND CONTRACTS 1 (July 16, 1982).

[22] *Id.*

[23] *Id.*

[24] PROTECTING HUMAN SUBJECTS, *supra* note 1, at 82-83; *see also* Appendices G and H, *id.* at 231, 261.



that extensive new regulations be developed; rather, it suggested greater uniformity in the application of existing regulations.

Association of American Medical Colleges. The problems of misconduct in biomedical research that were discussed in the First Biennial Report and in the Workshop on "Whistleblowing" also received attention during 1982 from the Association of American Medical Colleges. In January the AAMC convened an Ad Hoc Committee on the Maintenance of High Ethical Standards in the Conduct of Research, chaired by Dr. Julius R. Krevens, Dean of the University of California, San Francisco. It quickly prepared a report, which was adopted in June 1982 by the Executive Council of the AAMC and printed in pamphlet form for distribution to faculties of medical schools and teaching hospitals.[25]

The AAMC emphasized the importance of validity and accuracy to the scientific process, noting not only that dishonesty runs counter to the very nature of research but also that misconduct may erode public confidence in the scientific enterprise. The AAMC therefore urged academic faculties to "create a climate that promotes faithful attention to high ethical standards"[26] and to join with administrators in considering the following:

[25] *See* Association of American Medical Colleges, *The Maintenance of High Ethical Standards in the Conduct of Research*, Appendix C *infra*.
[26] *Id.*

- Having in place a conspicuous and understandable mechanism for dealing with instances of alleged fraud.
- Adopting institutional policies that define misrepresentation of research data as a major breach of contract between the faculty or staff member and the institution. (This policy should particularly be articulated in the faculty handbook.)
- Articulating institutional policies that foster openness of research.
- Encouraging faculties to discuss research ethics to heighten awareness and recognition of these issues.
- Establishing institutional policies to provide: 1) an appropriate and clearly defined locus of responsibility for the conduct of research; 2) assurance that individuals charged with supervision of other researchers can realistically execute their responsibility; and 3) particular attention to adequate supervision of large research teams.
- Assuring that quality rather than quantity of research is emphasized as a criterion for the promotion of faculty.
- Examining institutional policies on authorship of papers and abstracts to ensure that named authors have had a genuine role in the research and accept responsibility for the quality of the work being reported.
- Reviewing institutional policies on the recording and retention of research data to ensure that such policies are appropriate and are clearly understood and complied with by all faculty.
- Examining the institutional role and policies in guiding faculty concerning public announcement and publication of research findings.[27]

The AAMC also provided a Prototype of Procedures for Dealing with Alleged Fraud to assist institutions in developing their own procedures for processing initial reports of fraud, investigating reported fraud that appears upon initial review to be substantial, and taking action upon completion of an investigation.[28] In May 1982, Yale University formally adopted a Policy Statement on Collaborative Research that addresses many of the points identified by the AAMC (see Appendix C *infra*).

[27] *Id.*
[28] *Id.*

Reporting the Number of Human Subjects and the Incidence of Significant Adverse Effects

In preparing its report on *Compensating for Research Injuries*,[29] the Commission was disappointed to discover that no data are collected from which to determine either the number of human subjects involved in Federally supported research in a given year or the nature and incidence of serious injuries associated with such research. It recommended, therefore, that principal investigators whose work is supported by the Federal government be required to report such information as part of their annual reports. Although the Commission recognized the difficulty of developing a definition of "adverse effect" that would be useful in the reporting of significant injuries, it was confident that a definition could be developed over time—particularly since the Veterans Administration (VA) was in the process of testing such a reporting requirement.

After the publication of *Protecting Human Subjects*, however, the Commission learned from the VA that the definitional problems were so pervasive that the data collected during the first year of their reporting requirement were not useful. Because of concern expressed by the VA and the Association of American Medical Colleges, senior staff of the Commission continued to work with those organizations to develop a workable definition of reportable adverse effects. The Commission hoped that a reporting requirement might be included in the "core" policy to be adopted by all Federal agencies, following discussion by the Ad Hoc Committee. To date, the Commission has received no information on this matter.

Adoption of Regulations Governing Research with Children and the Mentally Disabled

In Recommendation (5), the Commission observed that it had been four years since the National Commission in fulfillment of its Congressional mandate, submitted to the Secretary of HEW recommendations concerning research involving children and those institutionalized as mentally infirm. Ethical concerns about these populations revolve around the issue of informed consent. Children, because of their age, are generally unable to provide legally effective informed consent. Those institutionalized as mentally disabled may or may not be able to give informed consent or their capacity may fluctuate over time. Current regulations permit them to be involved in research, even over their own express

[29] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, COMPENSATING FOR RESEARCH INJURIES, U.S. Government Printing Office, Washington (1982).

objections, if their parents or legal guardians give permission. The National Commission was keenly aware of the urgent need to conduct research on the causes, treatment, and prevention of pediatric diseases and of emotional and cognitive disorders, and it urged special protection for children and the mentally disabled so that research about such conditions might go forward in an ethically acceptable manner.

The legislation creating the National Commission clearly required the Secretary of HEW (now HHS) to respond promptly to the Commission's recommendations (within 180 days of their publication in the Federal Register). As noted in the First Biennial Report:

> Although no deadline for implementation of final regulations was set forth in the National Commission's enabling legislation, the President's Commission is certain that Congress anticipated an orderly and expeditious proceeding. Surely, it did not contemplate that the Department would prolong its rulemaking over a period of years.[30]

At its meeting on September 11, 1982, the Commission asked its HHS Liaison, Dr. Charles McCarthy, about the status of those two sets of regulations. Dr. McCarthy reported that final rules governing research involving children were in the Secretary's office awaiting action; the Commission wrote to Secretary Schweiker that it hoped "action will be forthcoming without delay."[31] On March 8, 1983, the special provisions for research on children were published in the Federal Register.[32]

Dr. McCarthy also suggested that the Department probably would not issue regulations governing research involving the mentally disabled in the foreseeable future.[33] The reasons given were twofold: current regulations already require IRBs to assure additional protections when subjects are likely to be vulnerable, and no consensus emerged regarding the 1978 proposed rules on this topic—instead, they were severely criticized by diverse groups.

Concerned that important studies on problems such as senile dementia of the Alzheimer's type might not be conducted because of the absence of Federal guidance on ethical issues, the Commissioners decided to write to HHS Secretary Schweiker urging that he "act expeditiously to remove regulatory ambiguities and impediments that may exist to research

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[30] PROTECTING HUMAN SUBJECTS, *supra* note 1, at 75-76.

[31] *See* letter from Chairman Morris B. Abram to Richard S. Schweiker, Secretary, U.S. Department of Health and Human Services (Sept. 16, 1982), Appendix F *infra*.

[32] 48 Federal Register 9814 (March 8, 1983).

[33] *See generally* transcript of 24th meeting of the President's Commission (Sept. 11, 1982), at 366-70.

with mentally disabled subjects under conditions that would assure ethical protection to those subjects."[34] The Commission noted in the letter that:

> We recognize the sensitivity and complexity of these areas of research, as did the Congress in 1974 in asking the National Commission to study these areas. We have also heard repeatedly that the absence of the necessary special provisions for these special research populations creates two problems. On the one hand, such subjects may be inappropriately exposed to risk in projects that do not receive review attuned to the particular problems of such research. On the other hand, some investigators, institutions and Federal funding officials may be unwilling to engage in research in the face of general Federal regulations and state law that they view as unclear and perhaps prohibitory, since no special provisions are made to protect these subjects who cannot give legally effective informed consent for themselves.

The Chairman of the former National Commission for the Protection of Human Subjects, on learning of the likelihood that no regulations for research with the mentally disabled would be forthcoming, also protested the Department's inaction.[35]

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[34] *Supra* note 30.

[35] It is imperative that important research not be left stranded because of doubts about its ethical acceptability; federal standards would remove many of those doubts. Further, as you are aware, the National Commission was created partly in response to research performed on the mentally retarded that many in our society found morally reprehensible. Such research would still be permissible under current HHS regulations. Nothing in 45 CFR 46 prohibits the enrollment of mentally disabled persons as research subjects against their expressed wishes or in studies totally unrelated to their condition. I cannot believe that you find this acceptable policy for your department.

The U.S. Congress clearly intended that the Commission's recommendations be adopted unless there were cogent reasons, articulated by the Secretary of your Department, not to. I do not believe that a lack of consensus is sufficient justification for modifying the Commission's well-considered recommendations; it certainly cannot justify a decision to decline to issue any regulations whatsoever. Federal regulations would not only protect those human subjects, they would also assist the scientific community by providing guidelines for the ethical conduct of research on the mentally disabled.

Letter from Kenneth J. Ryan, Chairman, Department of Obstetrics and Gynecology, Harvard Medical School, to Richard S. Schweiker, Secretary, U.S. Department of Health and Human Services (Oct. 4, 1982), Appendix F *infra*.

On December 16, 1982, Secretary Schweiker responded that, while continuing "to consider specific issues regarding protections" for institutionalized mental patients, the Department "is not intending to issue additional regulations in the near future."[36] He provided two justifications: first, that the rules proposed by the Department in November 1978 had produced a "lack of consensus," and, second, that the basic regulations on human subjects research adequately respond to the recommendations made by the National Commission to protect persons institutionalized as mentally disabled.

Despite the broad support apparently enjoyed by the National Commission's recommendations on this subject,[37] the Department decided to depart from them. Although the complexity of the alternative wording offered by the Department may account for some of the negative responses, others apparently result from the Department's departures from the Commission's recommendations, especially the addition of "consent auditors" or "subject advocates" even for potential subjects capable of understanding and consenting to research involving no more than minimal risk.[38] Moreover, similarly adverse public reaction to the 1978 proposals on children's research did not prevent the Department from eventually

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[36] Letter from Secretary of Health and Human Services Schweiker to Morris B. Abram (Dec. 16, 1982), Appendix F *infra*.

[37] The National Commission conducted public hearings and received both oral testimony and written reports from public interest groups, physicians and scientists, research administrators, lawyers, ethicists, and other scholars. The members of the Commission visited institutions for the emotionally disturbed and the mentally retarded, deliberated at length in public meetings, considered opinions submitted in writing by many members of the public and interested professional organizations, and finally, submitted a series of well-considered recommendations to HEW Secretary Califano on February 2, 1978. Those recommendations, along with the Commission's report on its studies and deliberations, were published for public comment on March 17, 1978, 43 Federal Register 11328. In the preamble to the Department's own proposed rules of November 17, 1978, Secretary Califano reported that:

> In response to publication in the *Federal Register* of the Commission's recommendations on research involving those institutionalized as mentally infirm, approximately 100 comments were received from individuals, citizens groups, legal and medical practicioners, researchers, and representatives of societies, university departments, and institutions. Although the respondents objected to some points in the recommendations, they were mainly complimentary of the Commission's recommendations. Several indicated complete acceptance of the recommendations as drafted.

43 Federal Register 53953 (Nov. 17, 1978).

[38] See 43 Federal Register 53952 (Nov. 17, 1978).

issuing revised provisions that overcame critics' main concerns.

The Department's second reason for neither adopting some form of regulations for research on mental patients nor proposing a revised set of rules for new comments is equally as puzzling as its first reason. Section 46.11(b) of the regulations,[39] which is cited in Secretary Schweiker's December 16, 1982, letter, simply advises Institutional Review Boards (IRBs) to assure that "appropriate additional safeguards have been included in the study to protect the rights and welfare of the subjects" when persons with acute or severe physical or mental illness are to be included as subjects of research. No guidance is given as to what those additional safeguards might be; moreover, the provision of "additional safeguards" is solely in the context of limiting risks, not other mportant considerations. It does not address the problems surrounding consent for the involvement of emotionally disturbed or mentally retarded individuals in research activities, nor does it place limits, such as those recommended by the National Commission, against including such persons as a general matter in research unrelated to their condition or on the amount of risk to which they may be exposed in research that is "nontherapeutic" (that is, not designed or likely to provide any direct health benefit to the subjects). Such concerns presumably were still to be addressed by the rules governing research with the mentally disabled, which, the Department has repeatedly stated, are still under consideration.

When the current regulations governing research with human subjects were first proposed, the Department noted that regulations were already in place to protect some "special groups" (fetuses, pregnant women, and prisoners), while regulations proposed for others "who may have diminished capacity," including those institutionalized as mentally disabled, "are being withheld pending further comment on them as well as the proposed [general] regulations." When the final rules were published in January 1981, the Department repeated that:

> [R]egulations have been proposed to provide additional safeguards for other (sic) who may have diminished capacity. These were Research Involving Children...and Research Involving Those Institutionalized as Mentally

[39] Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe mental illness, or persons who are economically or educationally disadvantaged, [the IRB shall determine that] appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects. 45 CFR 46.111(b).

> Disabled....Final regulations on these two categories are still being considered by the Department.[40]

Thus, under present regulations, no special guidance is provided regarding the ethical acceptability of involving such subjects in research unrelated to their condition, or in research presenting more than minimal risk; nor is any specific guidance provided regarding who may consent for such persons to be involved in research and the conditions, if any, under which they may be included over their express objections. Although the regulations permit consent by a person's "legally authorized representative," the definition provided is not particularly illuminating with respect to who might act in such a capacity.[41]

One of the concerns in this field—which has surfaced, for example, in discussions of the need for, but ethical uncertainty of performing, research with Alzheimer's dementia patients—is whether an IRB might feel more sure of its judgment if backed up by a national review body. Review by a national Ethics Advisory Board (EAB) is currently required for certain types of research involving the human fetus, products of human *in vitro* fertilization, and prisoners.[42] The National Commission recommended that research proposed for funding by HHS on mentally disabled patients be allowed to proceed, even if it presents more than minimal risk and no likelihood of benefit to the participating subjects, if an IRB deems the research likely to produce knowledge of major significance for the solution of a serious health problem affecting children or the mentally disabled, and if an EAB so advises.[43]

In the National Commission's opinion, review of ethically problematic protocols by a national interdisciplinary board would provide an opportunity for public participation as well as a careful examination of the relevant legal, ethical, scientific, and social issues. This would protect vulnerable subject populations in two ways. First, it would assure that they are rarely involved in research presenting more than minimal risk (and no direct therapeutic benefit) and only in research carefully scrutinized at the national level. Second, it would provide a mechanism for permitting important research to be conducted that might otherwise be disapproved because of doubts about its ethical acceptability. Since the EAB was abolished early in 1980, however, there is currently no mecha-

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[40] 46 Federal Register 8366 (Jan. 26, 1981).

[41] 45 CFR 46.102(d) defines a "legally authorized representative" as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."

[42] 45 CFR 46.211 and 46.306.

[43] 43 Federal Register 2084, 2087 (Jan. 13, 1978); 43 Federal Register 11334 (March 17, 1978).

nism for providing HHS with ethical review and advice on such matters at the national level.

Extending Regulations to "Private" Research Organizations Receiving Direct Congressional Appropriations

Recommendation (6) was addressed to the Congress to provide statutory assurance that "private" research institutions, funded by direct Congressional appropriations, would comply with regulations for the protection of human subjects. The Commission has been informed by its HHS Liaison that the Gorgas Memorial Institute for Topical Diseases, the entity that prompted the recommendation, has since voluntarily entered into negotiations with NIH for an approved "assurance of compliance" with the HHS regulations.[44] That removes the initial impetus for the recommendation. As Congress may, however, from time to time provide research support directly to other organizations, the recommendation that such funds be conditional upon compliance with regulations for the protection of human subjects remains valid.

Summary

Overall, the response of Federal agencies to the recommendations of the Commission's 1981 Report has thus far been uneven. Although there was considerable reason for optimism at the beginning of 1982, less has been accomplished than was promised by the Federal officials charged with responding to the Commission's recommendations. A number of agency responses seem to have become stalled in the bureaucracy despite the good intentions of all concerned; others are languishing for obscure reasons.

The Commission regrets that, because of these delays, it will not have an opportunity to comment on more responses and thus to participate in what augurs to be a constructive process of resolving remaining issues.

[44] Letter from Charles R. McCarthy to Barbara Mishkin (Dec. 23, 1982).

Commission Activities in 1982

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The Commission's activities in the area of protecting human subjects were focused this year primarily on (1) developing a guidebook for IRB members and (2) testing peer site visits as a method of evaluating and improving the performance of IRBs. The Commission also identified areas of concern that should be resolved but that time did not permit it to address. Finally, senior staff worked with officials in HHS and the Ad Hoc Interagency Committee on Protecting Human Subjects to assist in implementing some of the Commission's 1981 recommendations.

The IRB Guidebook

The series of IRB hearings held by the National Commission for the Protection of Human Subjects showed conclusively that IRBs both need and want additional guidance on fulfilling their responsibilities. HHS had been planning to develop commentaries on the regulations as part of its education program once the amended regulations were issued in January 1981. On the advice of a group of consultants convened in the fall of 1980, the President's Commission decided to collaborate with OPRR to develop a guidebook for IRBs that would go beyond an explanation by exploring varying positions taken by commentators and suggesting points to consider in IRB review.

Initial portions of the guidebook were developed under a contract with Public Responsibility in Medicine and Research (PRIM&R), a Boston-based, nonprofit organization that sponsors annual conferences on subjects related to the protection of human subjects; PRIM&R also publishes educational materials of general interest to IRBs. The materials generated were reviewed by an editorial board comprised of several members and senior staff of the Commission, officials of NIH and FDA,

research scientists, and IRB members and administrators from outside the Federal government. Extensive revisions, based upon the editorial board's comments and criticisms, were undertaken by Commission staff with additional assistance by staff at NIH and FDA. Meanwhile, the NIH Office for Protection from Research Risks developed commentaries on the new regulations, in collaboration with the Office of the Associate Commissioner for Health Affairs at FDA.

The guidebook includes the following sections in a loose-leaf binder:

Background: This section will be particularly useful for new IRB members and for investigators just beginning their clinical research and in need of a basic understanding of the background and purposes of the IRB review system.

Regulations and Commentary: This section will assist in resolving uncertainties about the intent or interpretation of regulatory provisions. It should also be a useful reference for initial reviewers of research proposals.

Administration of an IRB: This section is directed primarily at institutional administrators and IRB Chairmen. It will also be of interest to lay members and to others on the IRB concerned about how the IRB relates to other institutional offices. A list of suggested materials for an IRB library is included.

Research goals and procedures: This section describes research subject matter, goals, and methods in a general, introductory way and provides references for further reading. It will be of most benefit to nonscientists on the IRB and to scientist-reviewers who are confronting a research proposal in a discipline with which they are unfamiliar, *e.g.*, the biochemist member of an IRB reviewing a proposal in sociology.

Considerations of research design: This section describes and provides information on the reasons for using certain experimental designs. The ethical issues raised by such use are also explored.

Basic IRB Review: This section takes up where the commentary to the regulations ends. It presents the major focal points of IRB review: informed consent, risk/benefit analysis, privacy and confidentiality, selection of subjects, and incentives for participation. It goes beyond the actual regulations to indicate how the regulations might be applied in various situations. It will be of great assistance to new IRB members, primary reviewers, and research scientists trying to understand what the IRB concerns are and how to respond to them.

Special classes of subjects: This section provides an analysis of the ethical issues that arise in research

involving classes of particularly vulnerable research subjects. Regulations dealing with some of these categories are already in force; for others, regulations are pending and for still others, none are anticipated.

Forms: Included are samples of HHS forms (required for submission of research proposals, annual review, etc.), examples of consent forms, forms for principal investigators' submission for IRB review, etc.

Local IRB organizational documents: This is a place to insert documents pertaining to each institution and its IRB—the institutional assurance, current list of IRB members and staff, statements of meeting procedures, review procedures, the institution's standard forms, etc.

Glossary: This explains terms of art used in the context of reviewing biomedical and behavioral research. Lay members will find this section particularly useful; scientists also may turn to the glossary for clarification of terms germane to disciplines with which they are not totally familiar. For example, a biochemist might find the definition of "field work" helpful, while a social scientist might welcome an explanation of "Phase I drug trials."

Copies of the guidebook will be mailed early in 1983 to all IRBs with approved assurances on file at NIH, to members of the Pharmaceutical Manufacturers Association, and to persons on the Commission's mailing list who have requested a copy. Additional copies will be available from the NIH Office for Protection from Research Risks.

IRB Site Visits—An Exploratory Study

The National Commission recommended in 1978 that NIH implement procedures to monitor the performance of IRBs. In the intervening years, however, the NIH Office for Protection from Research Risks has been developing new regulations to implement other recommendations of the National Commission, so there has been little time to develop systematic procedures for monitoring the performance of IRBs.

FDA has had a formal system of periodic inspections of IRBs since 1977; however, various criticisms have been lodged by IRB members and research administrators about the FDA's inspection procedures. A recurrent suggestion has been that IRBs be evaluated by site visits conducted by peers (*i.e.*, other IRB members and administrators). The Commission undertook a pilot study of such an approach under the direction of Bradford Gray, Ph.D., a special consultant. A description along with a summary of the findings and conclusions of the study.

Additional Activities

The Commission, through its Chairman, corresponded with HHS Secretary Schweiker concerning the Department's proposal to exempt certain social policy experiments from the requirements of 45 CFR 46 for IRB review and informed consent. Programs for which social policy experiments would be exempt from IRB review under the HHS proposal include Medicare, Medicaid, Aid to Families with Dependent Children, Head Start, Developmental Disabilities, Child Abuse Prevention and Treatment, the Native Americans Program and the Social Security Disability Amendments of 1980. The HHS proposal to exempt all such research from IRB review (47 Federal Register 12276, March 22, 1982) was met with sharp criticism by a number of public interest groups including the Leadership Conference on Civil Rights, the Children's Defense Fund, and the Gray Panthers.

The Commission urged that IRB review be required for any social experimentation involving the restriction or limitation of benefits to which the subjects would otherwise be entitled by law (and that would continue to be provided to individuals not involved in the research). This would ensure that the risks of the research are justified by the benefits anticipated, and that the research is well designed and thus the knowledge sought is likely to be obtained. On March 4, 1983, the Department announced its conclusions, adopting a slightly modified version of the proposed exemption. The HHS proposal, Commission correspondence, and HHS final rule appear in Appendix D *infra*.

Issues Worthy of Further Consideration

The Commission has also identified a number of unresolved issues relating to the protection of human subjects. Due to constraints of time and resources, and the full agenda already imposed by its legislative mandate, the Commission has been unable to address these issues. Nonetheless, they are important and should be addressed by an appropriate body as soon as practicable. This review could be provided by a government-wide coordinating group on human research, if one emerges from the present process of regulatory consolidation described in Chapter One, or by an ethics advisory board if such a body is reestablished within the Department of Health and Human Services.

It should be noted that an ethics advisory board would provide review by an interdisciplinary group of consultants, including representatives of the general public, whereas an interagency coordinating council would not. In addition, meetings of an Ethics Advisory Board would be open to the public, whereas meetings of a group composed entirely of Federal

employees need not be. A brief review of the issues is presented here as a starting point for whatever body assumes the task of addressing them.

The Extension of Federal Regulations to Non-Federally Funded Research. The National Research Act of 1974 requires IRB review of Federally sponsored research with human subjects. However, the language of the Act is ambiguous about Federal oversight of non-Federally supported research. Section 212 of that Act amended the Public Health Service Act by adding the following provision:

> SEC. 474. (a) The Secretary shall by regulation require that each entity which applies for a grant or contract under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an 'Institutional Review Board') to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research.

Many people (including officials at HHS) interpreted the language of section 474 to require IRBs to review *all* research conducted at such institutions. In fact, although HEW regulations in 1974 were applicable on their face to research supported by the Department, grantees and contractors were, as a matter of policy, required to assure HEW that their IRBs reviewed *all* research involving human subjects.[1]

The National Commission for the Protection of Human Subjects concluded that all research conducted under the auspices of an institution receiving Federal research grants or contracts should be subject to the same review standards as HHS-funded research and recommended that the necessary legislation be enacted.[2] The National Commission believed that the principle of equal protection would be violated if subjects in one research project were afforded less protection than subjects in another—at the same institution—because of differences in funding mechanisms. Such a double standard would also suggest that IRBs are important only for meeting

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[1] National Commission for the Protection of Human Subjects, REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, APPENDIX, U.S. Government Printing Office, Washington (1978) at 2-1.

[2] National Commission for the Protection of Human Subjects, REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, U.S. Government Printing Office, Washington (1978) at Recommendation (l)(C) at 3.

Federal requirements rather than because of the nature of their work.

In proposed amendments to its regulations, designed to implement the recommendations of the National Commission, HHS articulated what had been an informal policy to require IRB review for all research at institutions receiving PHS grants and contracts. The ensuing controversy led the President's Commission to examine the proposal and, in September 1980, the Commission advised HHS Secretary Harris that the language of the 1974 National Research Act did not provide adequate Congressional authority to extend HHS regulations beyond those activities actually funded by the Department's research grants and contracts.[3] In the revised regulations published in January 1981, the Department formally withdrew its requirement that grantee and contractor institutions apply HHS regulations to all research conducted under their auspices.[4]

The question remains, however, whether Congress *should* give Federal agencies authority to extend their regulations to non-Federally funded research activities. Although the argument of equal treatment seems strong in the context of medical research, it has been challenged vigorously by behavioral and social scientists who believe that extension of prior review requirements to non-Federally funded surveys and questionnaires violates the First Amendment's protection of free speech.[5] Since most of the activities of concern to social scientists are now exempt from the regulatory requirements, the issue is not so pressing as it was originally. Concerns continue to be raised, however.[6]

To resolve these questions, issues of both fact and principle will need to be considered. For example, to what extent do research institutions now requiring IRB review of *all* research protocols, regardless of source of funding? A 1974-75

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[3] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, PROTECTING HUMAN SUBJECTS, U.S. Government Printing Office, Washington (1981) at 165-75.

[4] 46 Federal Register 8366-69 (Jan. 26, 1981).

[5] E.L. Pattullo, *Reconciling Risk and Regulation*, 18 SOCIETY 34 (1980); Ithiel de Sola Pool, *The New Censorship of Social Research*, 59 THE PUBLIC INTEREST 57 (1980); John W. Peltason *et al., Comment on the Proposed Regulations from Higher Education and Professional Social Science Associations*, 2 IRB 10 (Feb. 1980); John A. Robertson, *The Law of Institutional Review Boards*, 20 UCLA L. REV. 484, 498-510 (1979); John A. Robertson, *The Scientist's Right to Research: A Constitutional Analysis*, 51 S. CAL. L. REV. 1203 (1978).

[6] E.L. Pattullo, *How General an Assurance?*, 3 IRB 8 (May 1981); Judith Jarvis Thomson *et al., Regulations Governing Research on Human Subjects: Academic Freedom and the Institutional Review Board*, ACADEME 358 (Dec. 1981).

survey of IRB practices conducted for the National Commission revealed that in all hospitals and medical schools surveyed the IRBs reviewed research not funded by HEW, but in universties only 75% of IRBs (which reviewed more social science projects) did so.[7] What are the Federal interests in non-Federally funded research that would justify insisting that institutions apply Federal standards to all research projects?

The Relation between IRBs and Study Sections (Scientific Review Groups). IRB review is considered complementary to the review process used by Federal agencies to assess the scientific merit and importance of proposed research.[8] Such Federal agency assessments are performed by scientific review groups or "study sections" made up of consultants with expertise in particular research fields. IRBs, on the other hand, are located at the research institution and include both lay and scientific members. The IRB is expected to review all types of research that fall under its purview.

In 1978, as the National Commission was coming to a close, it became aware of certain tensions between IRBs and study sections.[9] This tension stemmed from a growing tendency for study sections to concern themselves not only with the scientific merit of proposals but also with such ethical issues as risk/benefit acceptability and informed consent. In some cases, Federal agencies were assigning this responsibility to study sections, while in other cases study sections were following the wishes of particular study section members. Some researchers and IRBs began to complain that their ethical decisions were being "second-guessed" by study sections. This seemed to cast doubt on the importance of the work performed by IRBs; it was also seen as inefficient, since study sections do not have the same opportunity as IRBs to clarify or resolve questions of ethics informally through consultation with the principal investigator. In addition, critics argued that study sections, while eminently qualified to perform scientific assessment, have less competence for ethical review than do IRBs.[10] The resultant system, it was argued, undercut the authority of

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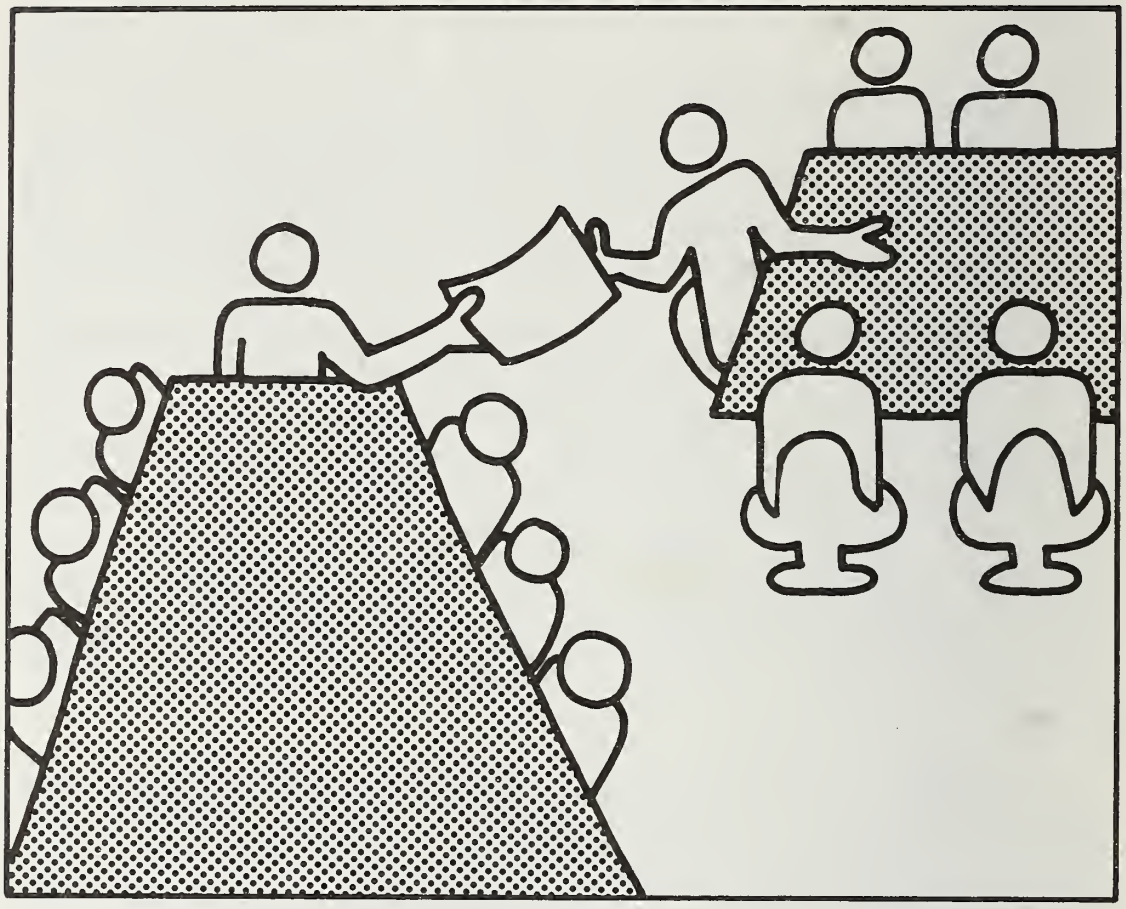
[7] Report and Recommendations: Institutional Review Boards, Appendix, *supra* note 1, at 1-31. OPRR reports informally that of the first 200 new multiple project assurances negotiated, all commit the IRB to review non-Federally funded research.

[8] Mortimer Lipsett, John Fletcher, and Marian Secundy, *Research Review at NIH*, 9 Hastings Ctr. Rep. 18 (Feb. 1979).

[9] Transcript of 42nd Meeting of the National Commission for the Protection of Human Subjects (June 10, 1978), National Technical Information Service, Springfield, Va., at 188-227.

[10] Robert J. Levine, *The Impact of Institutional Review Boards on Clinical Research*, 23 Perspectives in Biology and Medicine S98 (1980); Robert J. Levine, *Changing Federal Regulation of IRBs, Part II: DHEW's and FDA's Proposed Regulations*, 1 IRB 1 (Nov. 1979).



IRBs, introduced poorly informed or irrelevant ethical objections to proposed research, and produced unjustified delays by causing deferral of decisions on proposals.

On the other hand, because expertise in specialized areas of research is the major criterion for selection of members of study sections, study sections may be more technically competent than IRBs to assess the risks in highly specialized fields. A proposal might be reviewed by an IRB without a full appreciation of its risks. Furthermore, it is difficult to imagine any system that makes no errors, and the IRB system, as is discussed elsewhere, is not only decentralized—it also operates with very little quality control. Thus, the argument goes, shouldn't a study section raise ethical issues when they are encountered? And might not study sections be particularly useful in recommending ways to reduce or contain the risks presented in proposed research?

Since the mid-1970s, as described more fully in Chapter Three of this Report, HHS has required study sections to consider specific ethical as well as scientific aspects of research in their review. Perhaps the uncertainty about the proper relation between IRBs and study sections has been reduced by that action. On the other hand, some IRBs continue to object both to the procedure and to the substance of the decisionmaking of study sections. Futher efforts by HHS to reduce the negative effects of study section review of ethical issues seems warranted.

Research Involving the Comatose and Cadavers

Research on the comatose. Advances in emergency medical care have resulted in patients who survive an initial crisis but who may remain in a permanently comatose or vegetative state. This, in turn, has generated concern both about how such patients should be treated and about how to improve emergency care to achieve better outcomes. Research on emergency care, however, presents serious problems inasmuch as emergency patients are often unconscious and it may not be possible to locate family members in time to obtain their consent to whatever intervention is contemplated. Recent studies, for example, have demonstrated that the immediate administration of certain drugs to victims of head truama and cardiac arrest will reduce the likelihood of permanent neurological deficits.[11] The patients to whom the drugs must be administered, however, are not conscious at the time such treatment should take place; and unless a family member accompanies the patient to the hospital, there may be insufficient time to obtain consent for treatment (standard or otherwise) from anyone.[12]

It is settled law that physicians and hospitals may assume that an emergency patient would consent to life-saving treatment; such treatment may therefore be initiated without express consent. The legal principle is based, however, on the provision of standard care. It is not so clear, however, whether one should assume that an emergency patient would consent to participation in research on new or experimental treatment.[13]

Research on the "brain-dead" and other cadavers. There have been suggestions in recent literature that patients who are declared dead based upon complete cessation of brain functions, but whose respiration and circulation are artificially maintained, would make good subjects for certain kinds of research.[14] The notion is that "risk" has no meaning for the deceased; therefore, they cannot be "harmed" by the administration of experimental drugs and medical devices or by trials

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[11] Katherine Detre *et al., Collaborative Randomized Clinical Study of Cardiopulmonary-cerebral Resuscitation*, 9 CRIT. CARE MED. 395 (1981).

[12] Norman Fost and John Robertson, *Case Study: Deferring Consent with Incompetent Patients in an Intensive Care Unit*, 2 IRB 5 (Aug./Sept. 1980); Tom L. Beauchamp, *Commentary, id.* at 6.

[13] Norman S. Abramson, Alan Meisel, and Peter Safar, *Informed Consent in Resuscitation Research*, 246 J.A.M.A. 2828 (1981).

[14] Willard Gaylin, *Harvesting the Dead*, 249 HARPERS 23 (Sept. 1974); Norman Fost, *Research on the Brain Dead*, 96 J. PEDIATRICS 54 (1980); Ronald A. Carson, Jaime L. Frias, and Richard J. Melker, *Case Study: Research with Brain-Dead Children*, 3 IRB 5 (Jan. 1981); Robert M. Veatch, *Commentary, id.* at 6; John A. Robertson, *Case Study: Research on the Brain-Dead*, 2 IRB 4 (April 1980); David H. Smith, *Commentary, id.* at 6.

of radical forms of surgery. Further, society would benefit from the ability to test certain interventions without risk of harm to living human subjects.

On the other hand, although cadavers are used for many research and training purposes, there is something distinctly disquieting about maintaining certain functions of deceased persons solely to benefit "science." Moreover, since the maintenance of respiration and circulation gives the appearance of life, experimentation on the deceased may be extremely disturbing for any family members in attendance.

In its *Report and Recommendations: Research on the Fetus*, the National Commission for the Protection of Human Subjects recommended that research on the dead fetus be permitted "consistent with local law, the Uniform Anatomical Gift Act and commonly held convictions about respect for the dead."[15] It would appear necessary to require IRB review in order to determine whether the proposed research does, in fact, conform to "commonly held convictions." Yet current regulations governing research with human subjects apply only to research involving *living* human beings.

The Uniform Anatomical Gift Act provides for the donation of all or part of a decedent's body for medical or dental education, research, advancement of medical or dental science, therapy, or transplantation. Donations may be made by the donor, at any time prior to death, or by specified members of the family (or a guardian) in the absence of an express gift—or expression of contrary intention—by the decedent. Nothing in the UAGA limits the use of the bodies unless expressly limited by the terms of the gift (*e.g.*, donation of only a particular organ). If only a part of the body is donated, removal must be effected "without unnecessary mutilation" and the body then given over to the next of kin for burial.

Despite the apparent authority to use an unrestricted gift of a decedent's body without limitation, certain kinds of research activities are so unusual that donors may not be expected to have contemplated such use. The National Highway Traffic Safety Administration (NHTSA), for example, has strapped cadavers in automobiles to determine the effects on passengers of crashes at specified rates of speed. Cadavers have also been used to determine the effects on pedestrians of being struck by cars.[16] Following Congressional hearings on the legal and ethical acceptability of such experiments, NHTSA

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[15] National Commission for the Protection of Human Subjects, REPORT AND RECOMMENDATIONS: RESEARCH ON THE FETUS, U.S. Government Printing Office, Washington (1975) at 75.

[16]:3pIn Brief, *Using "Human Surrogates" on the Road to Better Bumpers*, 11 HASTINGS CTR. REP. 3 (Dec. 1981).

issued guidelines requiring all such research to be reviewed and approved by an IRB.[17] Moreover, those conducting the research are expected to make a reasonable effort to obtain specific consent from next of kin when the research is "beyond the normal scope of teaching and research as defined by appropriate local statutes." The President's Commission is not aware of any similar provisions in the rules of other Federal agencies. Given the kinds of research that might conceivably be conducted on the deceased, we suggest that consideration be given to requiring IRB review of certain kinds of such research to determine whether, in the words of the National Commission, it is consistent with "commonly held convictions about respect for the dead."

Therapeutic Intent in "Phase 1" Drug Testing in Cancer Chemotherapy. The attention of Congressional committees and the press in 1981 to informed consent in cancer research spotlighted a problem regarding early "Phase 1" testing of new anti-cancer drugs. In its formal regulations, the FDA defines the first two stages of drug research as follows:

> Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorbtion, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; Phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes.[18] In non-cancer studies, Phase 1 drug tests are usually conducted with healthy volunteers, so that pathological conditions are not present that might interfere with the measurement of the drug's activity in the human body. In such cases, it would be inaccurate to suggest that the subjects should expect any health benefit from their participation in the research.

With anti-cancer drugs, however, drug toxicity is so high that Phase 1 tests are usually conducted on persons with cancer, often desperate patients for whom all other possible treatments have proven unavailing. This is explained in the FDA's guidelines on "General Considerations for the Clinical Evaluation of Drugs":

> Phase 1 clinical pharmacology is intended to include the initial introduction of a drug into man. It may be in the usual "normal" volunteer subjects to determine levels of toxicity, and when appropriate, pharmacologic effect and be followed by early dose-ranging studies in

[17] National Highway Transportation Safety Administration (NHTSA), Washington, Order No. 700-4 (1979).

[18] 21 CFR § 321.l(a), *see* para. 10(a) of Form FS-1571 described therein.

> patients for safety and in some cases early evidence of effectiveness.
>
> Alternatively, with some new drugs, for ethical or scientific considerations, the initial introduction into man is properly done in selected patients. When normal volunteers are initial recipients of a drug, the very early trials in patients which follow are also considered part of Phase 1.[19]

The possibility that Phase 1 studies of anti-cancer drugs may (but need not necessarily) include an evaluation of therapeutic effect is described in FDA's "Guidelines for Clinical Evaluation of Antineoplastic Drugs":

> Phase 1 subjects have histologically confirmed malignant disease which at the time of the study is no longer amenable to conventional form(s) of therapy or for which there is no accepted standard treatment.... Because Phase 1 studies need not be designed for determination of therapeutic effect, research subjects need not have objectively measurable tumors. However, when measurable disease is present, the design of the study should be such that the therapeutic effect of the drug may be assessed.[20]

There remains some confusion as to whether Phase 1 tests of new cancer drugs can be described as always "therapeutic" for the patients who will be asked to participate as subjects. IRB members at times disagree on this question,[21] but cancer researchers have testified that they always have therapeutic intent in conducting Phase 1 tests of anti-cancer drugs.[22] Further, in a letter to Representative Henry Waxman (commenting on testimony of the Commission's staff), Edward Brandt, Assistant Secretary for Health, wrote:

> Notwithstanding the fact that some individuals within HHS may not concur, the official position of the

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[19] Food and Drug Administration, GENERAL CONSIDERATION FOR THE CLINICAL EVALUATION OF DRUGS, U.S. Government Printing Office, Washington (1977) at 6.

[20] Food and Drug Administration, GUIDELINES FOR THE CLINICAL EVALUATION OF ANTINEOPLASTIC DRUGS, U.S. Government Printing Office, Washington (1981) at 3.

[21] One IRB member reviewing the protocol for Phase 1 tests of MHTTF at M.D. Anderson indicated that it was a *therapeutic* research project; another, that it was *nontherapeutic*. *See* IRB review check lists of Alexander Y.M. Wang and Dr. W.W. Sutow, reflecting their review of protocol DT 78-31, discussed in PROTECTING HUMAN SUBJECTS, *supra* note 3, at 165-75.

[22] *See* Drs. Emil Freireich, James F. Holland, and John E. Ultmann, *Statements before Joint Hearing of Subcomm. on Health and the Environment, Comm. on Energy and Commerce, and Subcomm. on Investigations and Oversight, Comm. on Science and Technology, U.S. House of Representatives* (Oct. 27, 1981).

> Department, including NCI, NIH and FDA, is to regard Phase I trials of anti-cancer drugs as *potentially* therapeutic. The often small, but real possibility of benefit must be weighed against the nearly 100 percent probability of death if experimental therapy is not attempted for the advanced cancer patients who participate in Phase I studies.[23]

At a 1981 meeting of the HHS Secretary's Task Force on NCI/FDA [Regulation of] INDs (Investigational New Drugs), the Commission's Executive Director and Deputy Director urged that this definitional problem be given serious attention.[24] Perhaps the classifications or nomenclature of Phase 1 and 2 should not be applied to research on cancer chemotherapies. More important, attention should be paid to the ambiguity in the term "therapeutic research" as applied to the initial use of new anti-cancer agents in human beings, in research usually designed to test pharmacokinetic and toxiologic matters. It is important that patients who are asked to participate in tests of new anti-cancer drugs not be misled about the likelihood (or remoteness) of any therapeutic benefit they might derive from such participation. This was recently emphasized by the HHS Task Force on NCI/FDA regulation of new anti-cancer drugs and by a former director of the NIH Clinical Center.[25]

Diversion of Drug Research to Other Countries. When the Department of Health and Human Services issued regulations in 1978 effectively terminating drug testing in U.S. prisons, there was concern that pharmaceutical manufacturing companies would turn to foreign countries (especially in the Third World) for drug testing.[26]

In December 1981, however, the Food and Drug Administration issued proposed rules that would lift the restrictions on prison research and impose standards for the conduct of such research similar to those recommended by the National Commission for the Protection of Human Subjects.[27] If final

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[23] Letter from Edward N. Brandt, Jr., M.D., Assistant Secretary for Health, HHS, to the Honorable Henry A. Waxman, Chairman, Subcomm. on Health and the Environment (Nov. 20, 1981) at 3-4 (emphasis added).

[24] Task Force on NCI-FDA Investigational New Drugs, REPORT ON ANTICANCER DRUGS: THE NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION, U.S. Department of Health and Human Services, Washington (Jan. 28, 1982).

[25] *Id.* Vol. 2, at 72-73; Mortimer Lipsett, *On the Nature and Ethics of Phase 1 Clinical Trials*, 248 J.A.M.A. 941 (1982).

[26] William J. Broad, *Dollars for Drug Research Flow Overseas*, 205 SCIENCE 979 (1979).

[27] Food and Drug Administration, *Proposed Rules for Clinical Investigations Involving Prisoners as Subjects*, 46 Federal Register 61666 (Dec. 18, 1981).

rules to that effect are issued, drug research involving U.S. prisoners could resume if prisons meet those standards and are so certified. Therefore, diversion of drug research to foreign countries may be a moot point. On the other hand, on October 19, 1982, the FDA proposed amending its regulations to permit approval of new drugs based solely on data from clinical trials conducted outside the United States.[28] (Current regulations require at least one domestic study.) This may increase the proportion of drug research conducted abroad.[29] It is important to recognize that acceptance of data from properly conducted research from other countries avoids the necessity of submitting additional subjects to research procedures in order to repeat the studies in the United States.

The Commission suggests that the Pharmaceutical Manufacturers Association be asked to compare the proportionate amount of drug research now conducted overseas with that done, for example, five years ago. The PMA has cooperated fully in the past in conducting surveys of its members and providing detailed information to both the National Commission for the Protection of Human Subjects and this Commission, and there is every reason to believe that the Association would respond to such a request.

A related issue is the flexibility in review and consent requirements that should be permitted for research conducted in countries with cultures and social organizations distinctly different from those in the United states.[30] A 1980 report issued by the Institute of Medicine urged the President's Commission to recommend that appropriate and necessary modifications be permitted.[31] The World Health Organization and the Council for International Organizations of Medical Sciences (CIOMS) have recently developed a draft of research standards to be applied worldwide.[32] Implementation of those standards would dispel any fears of unethical research being conducted abroad, although the extent to which FDA could assure compliance is unclear. The rigor with which U.S. standards should be applied to research conducted abroad would have to be considered in light of any international standards that are adopted.

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[28] Food and Drug Administration, *New Drug and Antibiotic Regulations: Proposed Rules*, 47 Federal Register 46622 (Oct. 19, 1982).

[29] Stephen Budiansky, *U.S. Drug Market to Open Up?*, 299 NATURE 772 (1982).

[30] Carl E. Taylor, *Clinical Trials and International Health Research*, 69 AM. J. PUB. HEALTH 981 (1979).

[31] Institute of Medicine, U.S. PARTICIPATION IN CLINICAL RESEARCH IN DEVELOPING COUNTRIES, National Academy of Sciences, Washington (1980).

[32] World Health Organization and CIOMS, *Proposed International Guidelines for Biomedical Research Involving Human Subjects* (1982).

Journal Publication of Unethical Research. Briefly put, the question is whether unethical research can be discouraged by editorial policies refusing publication of the results or whether it is more instructive to publish the results of questionable research along with critical editorial commentary.[33] Furthermore, if the research is not published, additional subjects might be placed at risk in a replication of the ethically questionable study, which may well have been scientifically valid.[34] To publish papers based on unethical research (even with critical commentary), however, provides tangible rewards for the unethical scientists that some believe they should not receive.[35] This question involves First Amendment rights and is not really amenable to solution by Federal action. However, a properly constituted group might offer sound advice to scientific journals that have wrestled with this issue for a number of years.[36]

The Role of the Nonscientific and Unaffiliated Members of the IRB. HHS regulations require that each IRB be "sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds... and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel." More specifically,

> In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects,... the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects.[37]

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[33] Lois DeBakey, *Ethically Questionable Data: Publish or Reject?*, 22 CLIN. RES. 113 (1974); Lois DeBakey and Selma DeBakey, *Communication, Biomedical: Media and Medicine*, in 1 ENCYCLOPEDIA OF BIOETHICS, Free Press, New York (1978) at 180, 190-191.

[34] Robert J. Levine, *Ethical Considerations in the Publication of the Results of Research Involving Human Subjects*, 21 CLIN. RES. 763 (1973).

[35] Yvonne Brackbill and Andre E. Hellegers, *Ethics and Editors: Report of a Survey*, 10 HASTINGS CTR. REP. 20 (Feb. 1980); Arnold Relman, Erwin Neter, and Alfred Yankauer, *Commentaries, id.* at 22.

[36] Committee on Editorial Policy, Council of Biology Editors, *Ethical Experimentation and Editors*, CBE NEWSLETTER, Bethesda, Md. (1970); Lois DeBakey, THE SCIENTIFIC JOURNAL EDITORIAL POLICIES AND PRACTICES: GUIDELINES FOR EDITORS, REVIEWERS, AND AUTHORS, The C.V. Mosby Company, St. Louis, Mo. (1976); Alfred Yankauer, *Editor's Report: The Ethics of Publication*, 70 AM. J. PUB. HEALTH 218 (1980).

[37] 45 CFR 46.107.

Furthermore, each IRB must include at least one member whose primary concerns are in nonscientific areas (for example, lawyers, ethicists, members of the clergy) and each IRB must include at least one member who is not otherwise affiliated with the institution.

Although the regulations would appear to require considerable diversity among IRB members, they are apparently satisfied if the IRB includes one member who is a layperson, lawyer, or clergy unaffiliated with the institution. How many IRBs fulfill the requirement in this way is unknown. In addition, it is not clear what role such an individual should serve.

A variety of purposes or roles of nonscientist and community members on IRBs have been suggested: (1) to provide additional perspectives and offset professional narrowness of focus; (2) to provide advice on local laws, customs, values and attitudes; (3) to provide ethical analysis and guidance; (4) to represent the human subjects' interests; (5) to force scientists to examine their work—and their defense of their work—more critically; (6) to open the review process to community participation; (7) to enhance the confidence of the community in the research enterprise; and (8) to assist in assuring the adequacy and understandability of the information to be conveyed to prospective subjects. One might well ask whether a single individual can be expected to perform so many functions. One might also question the extent to which the inclusion of a single lawyer, member of the clergy, or a "community representative" (as they are sometimes called) fulfills any useful function in an IRB that may number as many as 15-25 people.

When local review was first initiated, it was in the form of peer review (*i.e.*, review by other scientists). In the mid-1960s, however, scholars began to examine more carefully the need for adequate review of research with human subjects and the concept that nonscientists should be included on review boards began to gain support. In 1971, the NIH *Guide to Grants and Contracts* suggested that the local ethics review committees "*may* need to include persons whose interests are in nonscientific areas" in order to determine the acceptability of research proposals in light of applicable law, community attitudes, and so forth.[38]

One concern may have been a perceived need to balance the narrow focus of the expert. As expressed by Harold Laski in 1931:

> Expertise, it may be argued, sacrifices the insight of common sense to intensity of experience. It breeds an

[38] National Institutes of Health, INSTITUTIONAL GUIDE TO DHEW POLICY ON PROTECTION OF HUMAN SUBJECTS, Bethesda, Md. (1971) at 4.

> inability to accept new views from the very depth of its preoccupaton with its own conclusions.... [T]he inference from a knowledge that the plain man is ignorant of technical details and, broadly speaking, uninterested in the methods by which its results are attained, is certainly not the conclusion that the expert can be left to make his own decisions.[39]

In the 1969 issue of *Daedalus*, in one of the earliest published materials on research with human subjects, William Curran suggested that perhaps NIH should encourage institutions to widen the membership of their review committees. He noted that lawyers would be useful for assuring adequate procedures and advising on matters of local law. The role of philosophers in discussing ethical issues was, he thought, equally clear; similarly, he believed that members of the clergy might be interested not only in ethical principles but also in particular religious beliefs and in the welfare of individuals (presumably, the research subjects). The role of other professionals, businessmen, and laymen he viewed as equally important, as

> forcing the professionals to interpret their deliberations and decisions to these general community representatives. Lay members will thus tend to transform the committee from closed associations of like-minded professionals who 'understand' one another into a more open forum of community responsibilit.[40] Curran also viewed IRB lay members as "consumers" sharing in community decisionmaking; and he suggested that perhaps research subjects should be included among members of review committees.[41]

The regulations and earlier NIH policy statements suggest that someone on the IRB should represent community attitudes. As Bernard Barber and his colleagues observed in 1973, however, it is hard to see how any one person could represent the "full diversity of the local community or the society."[42] Barber recommended that IRBs include "informed outsiders," knowledgeable about relevant laws, codes, and norms, as well as about the nature and purposes of biomedical research and survey techniques (useful for discovering the attitudes and values of a representative sample of the population). They also suggested that active participation of community members on

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[39] Harold J. Laski, *The Limitations of the Expert*, The Fabian Society, London (1931), excerpt *reprinted in* Jay Katz, EXPERIMENTATION WITH HUMAN BEINGS, Russell Sage Foundation, New York (1972) at 895.

[40] William Curran, *The Approach of Two Federal Agencies*, 98 DAEDALUS 583-84 (Spring 1969).

[41] *Id.*

[42] Bernard Barber ET AL., RESEARCH ON HUMAN SUBJECTS, Russell Sage Foundation, New York (1973) at 195.

such committees "might forestall the possibility of a hostile public reaction against biomedical research."[43]

The National Commission for the Protection for Human Subjects believed that "to guard against self-interest influencing or appearing to influence IRB determinations," at least one-third of the IRB members should be nonscientists.[44] They further noted that "it is desirable that the IRB show awareness and appreciation of the various qualities, values and needs of the diverse elements of the community served by the institution or in which it is located."[45] In Denmark, half the members of ethics review committees must be nonscientists; these lay members are appointed by the local county councils.[46]

More recently, attention has focused on the usefulness of lay members in assuring that the information to be conveyed to prospective subjects is both adequate and clearly presented.[47] Many IRBs seek the advice of their lay members on the wording of consent documents; indications are that they can be very helpful in this regard.

If all of the functions proposed for lay members are deemed important, perhaps more than one member of each IRB should be a nonscientist; perhaps more than one should be unaffiliated with the institution. Although HHS regulations require only one member of each IRB to be a nonscientist, most institutions have appointed more than one such member. In the 582 IRBs that operate under Multiple Project (General) Assurances there are at least 2066 nonscientists, an average of 28%, or more than three nonscientists per IRB.[48] These figures do not include social workers and other professionals who might also be considered nonscientists. Educational efforts should be made to encourage those IRBs that have only one nonscientific member to consider appointing more. Any IRBs experiencing difficulty in recruitment or attendance of non-institutional members might try scheduling evening meetings to avoid interfering with the occupational or childrearing responsibilities of such members. Further reflection on these matters

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[43] *Id.* at 196-97.

[44] Report and Recommendations: Institutional Review Boards, *supra* note 2, at 14.

[45] *Id.*

[46] Povl Riis, *Experience with Committees and Councils for Research Ethics in Scandanavia*, paper presented at the Research Ethics Symposium, Oslo, Norway (Aug. 1982).

[47] W. E. Waters, *Role of the Public in Monitoring Research With Human Subjects*, in National Institutes of Health, Issues in Research With Human Subjects, U.S. Government Printing Office, Washington (1980); Joan M. Ghio, *Inquiry: What is the Role of a Public Member on an IRB?*, 2 IRB 7 (Feb. 1980).

[48] Letter from Charles R. McCarthy, Director, OPRR, to Barbara Mishkin (Dec. 23, 1982). The data are based on 1982 information on membership provided to OPRR by IRBs.

would be useful. Perhaps the regulatory requirements for IRB membership and composition should be modified or explained more fully.

Evaluating the Performance of IRBs

II

The IRB System and Current Methods of Assessing IRB Implementation of the Regulations

3

The Commission's site visit project, described in Chapter Four, was based on the belief that more satisfactory ways could be found to assess the implementation of Federal rules for protection of human subjects and to improve the functioning of IRBs. This chapter discusses the system now used by two major Federal agencies that regulate research with human subjects.

The IRB System

The requirement for IRB review is now a standard feature of the regulations of Federal agencies that support or regulate research involving human subjects.[1] HHS requires IRB review and approval before it will support such research,[2] and the formal requirements of the HHS regulations are the basic model for most other Federal agency rules governing research with human subjects.

The regulations specify the substantive judgments that an IRB must make in reviewing proposed research (*e.g.*, that risks to subjects are minimized and are reasonable in relation to benefits anticipated from the research, that adequate provisions are made for informed consent and its documentation, that there are adequate plans for monitoring the data to insure the safety of subjects, and that adequate provisions are made for protecting the privacy of subjects and maintaining the confidentiality of data). IRBs are also responsible for assuring that appropriate additional safeguards are provided if the subjects are particularly vulnerable (*e.g.*, children or prisoners)

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[1] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, PROTECTING HUMAN SUBJECTS, U.S. Government Printing Office, Washington (1981) at 15-34.
[2] 45 CFR 46.

or are economically or educational disadvantaged, and that selection of subjects is equitable (*e.g.*, that one type of subject is not excessively involved in research that benefits others).

The Food and Drug Administration (FDA) has its own IRB regulations[3] for research performed in support of applications for approval of FDA-regulated products (such as drugs, biologicals, and medical devices). Under new FDA and HHS regulations published in January 1981, the IRB judgments to be made under the two sets of regulations are almost identical.[4]

There are important differences, however, between FDA and HHS approaches to assessing IRB implementation of their regulations. These differences concern both the establishment of IRBs and monitoring their activities.

Establishing an IRB

To meet HHS requirements, an IRB established by an institution seeking research support must be approved by the Office for Protection from Research Risks (OPRR) at the National Institutes of Health. This approval is based upon OPRR's review of a formal "assurance," which describes in detail how the institution will comply with the regulations. In its assurance, the institution must describe the composition of its IRB (which must satisfy certain membership requirements), describe procedures that the IRB will follow in reviewing proposed research, agree to provide continuing review of approved research and to report serious or continuing noncompliance by investigators with the requirements and determinations of the IRB, and agree to meet certain administrative, recordkeeping, and quorum requirements. OPRR maintains a list of IRBs that have provided satisfactory assurances of compliance.[5] Before a grant application for research with human subjects will be considered for funding, certification must be received that the research protocol has been approved by one of these IRBs.

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[3] 21 CFR 56; 21 CFR 50.20.

[4] The HHS regulations were published at 46 Federal Register 8366 (January 26, 1981) and the new FDA regulations were published at 46 Federal Register 8942 (January 27, 1981).

[5] OPRR actually negotiates two types of assurances of compliance with the regulations. IRBs created under "multiple project assurance" (formerly called general assurances) are authorized to perform review functions for all proposals coming from the institution. These IRBs, which are located at approximately 450 institutions, are relatively permanent. OPRR maintains and publishes a listing of these institutions. IRBs covered by "single project assurances" (formerly called special assurances) are created to review only a single project. Thus, they tend to be located at institutions at which relatively little research is conducted.

By contrast, FDA does not approve IRBs in advance and, accordingly, has no list of approved IRBs. Instead, a new product's "sponsor" (*i.e.*, a manufacturer or researcher who has developed a new pharmaceutical or medical device) is held responsible for meeting FDA regulatory requirements for development of new products and for eventual approval for marketing. One such obligation is to see that studies involving human subjects are reviewed by an IRB that meets the same basic requirements and makes the same basic judgments as those required by the HHS regulations. (A relatively small group, probably under 25%, of the IRBs reviewing FDA regulated research have assurances on file with OPRR.[6]) Before approving the initiation of human testing on new products, FDA requires that the manufacturer and research investigator sign formal promises to comply with regulatory requirements, including those that pertain to IRB review.

Assessing IRB Implementation of the Regulations

Though the FDA and HHS regulations contain basically the same requirements for the review of research, two contrasting methods are used in assessing their implementation. Compared to the HHS approach, FDA's approach is less centralized, more complex, and relies less on prior approval of IRBs and more on after-the-fact spot checks to monitor compliance.

The FDA Approach. The complexity of the FDA approach stems from its several regulatory programs—pertaining to drugs, biologics, medical devices, and so forth. In general, these regulations are administered by different bureaus—the Bureau of Drugs, the Bureau of Biologics, the Bureau of Devices. Although FDA has a single set of regulations for IRBs and informed consent, each bureau administers regulations—including those pertaining to IRBs—that relate to the products and substances for which it is responsible. Each bureau's procedures thus have some idiosyncratic features. However, in 1977 FDA developed an agency-wide "Bioresearch Monitoring Program" that has various coordinating, monitoring, and educational functions; its mission is to ensure the quality and integrity of research data submitted to the FDA and to assure the protection of human subjects in clinical trials.

FDA regulations apply to a variety of entities—the sponsors of research, clinical investigators, laboratories, and IRBs.

[6] According to materials provided by FDA to the Commission in October 1982, 27% of the 474 IRBs inspected to date by the Bureau of Drugs were on the OPRR list. It is believed that this is a larger percentage than among the IRBs that review research regulated by the FDA's Bureau of Devices, and may be similar to the IRBs reviewing research regulated by FDA's Bureau of Biologics.

Table 1:

FDA Inspections of IRBs, 1977-1983

Source: Office of the Associate Commissioner for Health Affairs, FDA.

Fiscal Year	IRB Inspections Completed
1977	55
1978	78
1979	319
1980	369
1981	352
1982	338*
1983	303*

* planned

For each of these, specific regulations and a compliance manual describe for FDA field investigators the steps involved in the audits or inspections that are conducted on a sample or spot check basis to monitor regulatory compliance. For sponsors, the inspection is designed to assure the validity of the research data and to determine such matters as whether the sponsor has met its reponsibilities for monitoring the research on the product under development. For clinical investigators, the inspections are designed to determine whether the investigator obtained IRB approval of studies involving human subjects and whether all subjects signed consent forms that had been approved by the IRB. For toxicological laboratories, inspections are designed to determine whether FDA regulations for good laboratory practices are being followed. Similarly, IRBs are inspected.

FDA has inspected IRBs for about a decade.[7] In the early 1970s most FDA inspections of IRBs took place when serious deficiences in the policies or procedures of an IRB were suspected. By October 1974, however, 25 IRBs had been inspected at randomly selected institutions including prisons, mental institutions, children's hospitals, university research centers, and nursing homes. These inspections revealed more deficiences than had been expected. In 1976, in response to a GAO report[8] and FDA's own findings of significant problems in both preclinical and clinical research, Congress instructed FDA to expand its monitoring of biomedical research conducted

[7] This description of FDA's IRB inspection program is based on materials provided in 1982 by the Office of the Associate Commissioner for Health Affairs, Food and Drug Administration, Washington.

[8] Comptroller General, *Federal Control of New Drug Testing Is Not Adequately Protecting Human Test Subjects and the Public*, U.S. General Accounting Office, Washington (1976).

under its regulations and provided resources for such efforts. FDA accordingly developed its Bioresearch Monitoring Program, and a more intensive program of IRB inspections was begun in April 1977. Table 1 shows the number of IRB inspections completed by the FDA since fiscal year 1977.

FDA conducts two kinds of IRB inspections: routine "surveillance" inspections and "directed" (or "for cause") inspections. Selection of IRBs for routine inspection is influenced by such factors as the type of study the IRB has reviewed (*e.g.*, a study of a hazardous device or a pivotal new drug) and the interval since (or results of) a previous inspection. Since FDA does not have a master list of IRBs (or of their characteristics), it is not possible to select IRBs for routine inspection systematically (*e.g.*, to inspect new IRBs within a year of their creation or to focus the program either on IRBs that review much FDA-regulated research or on IRBs that get little practice reviewing such research). A previously unknown IRB may come to light in various ways, such as through sponsor or clinical investigator inspections.

According to FDA, the timing of subsequent inspections depends on the findings of previous inspections. IRBs found to be seriously out of compliance will generally receive a directed inspection within six months. IRBs with minor deficiences will usually receive a subsequent routine inspection within two years. IRBs in full or substantial compliance will usually receive another routine inspection in two to three years.

Directed inspections arise out of some specific concern about the practices of an IRB. These may be problems identified either in earlier inspections of the IRB or in inspections of sponsors or clinical investigators (*e.g.*, if it was determined that a clinical investigator did not have IRB approval for a study).

Data released by FDA in 1980 provide some indication of the incidence of problems identified in IRB inspections and show that the frequency of these problems decreases at subsequent inspections[9] (see Table 2). The data were based on 100 IRBs that had most recently undergone both initial and subsequent inspections.

Although the data show IRB activities or practices that FDA sees as problematic occur rather commonly, little information was presented about the specific nature of the various types of problems. The lower incidence of problems found on second inspections suggests that many institutions make satisfactory changes as a result of the inspection program. FDA also reported a lower problem incidence at IRBs covered by a

[9] Transcript of *IRB Compliance Activity Workshop* held by FDA in Washington, Nov. 7, 1980, at 17-27.

Table 2:

Incidence of Different Types of Problems Identified on FDA Inspections of 100 IRBs

Source: Transcript of IRB Compliance Activity Workshop held by FDA in Washington (Nov. 7, 1980) at 2.

Problem Areas Inspection	IRBs with Problem at First Inspection	IRBs with Problem at Second
Informed Consent Forms	56%	43%
Continuing Review	40%	20%
Written Guidelines	40%	18%
Review of Informed Consent Procedures	36%	16%
Documentation of Committee Activites	29%	19%
Substantive Committee Minutes	22%	11%
Inadequate Material to Review	22%	8%
Procedures for Reporting Emergent Problems, Adverse Reactions, and Protocol Changes for IRB Review	22%	7%
Mail Review	20%	7%
Not Following Written Guidelines	19%	9%

general assurance of compliance with the HHS regulations than at other institutions.[10] It is not clear whether this was due to the assurance process per se or to the fact that general assurance institutions are larger and (presumably) that the IRBs there are more experienced.

FDA's inspections of IRBs are conducted by FDA field investigators. These investigators typically have a bachelor's degree with specialized course work, including a minimum of 30 hours of science. Field investigators are also trained in a variety of areas under FDA jurisdiction, such as drug and device production. Some have an area or two of particular specialization (such as drug manufacturing or the bioresearch monitoring program) in which they receive additional training (*e.g.*, in pharmacology or the conduct of clinical investigations).

[10] *Id.* at 19-23.

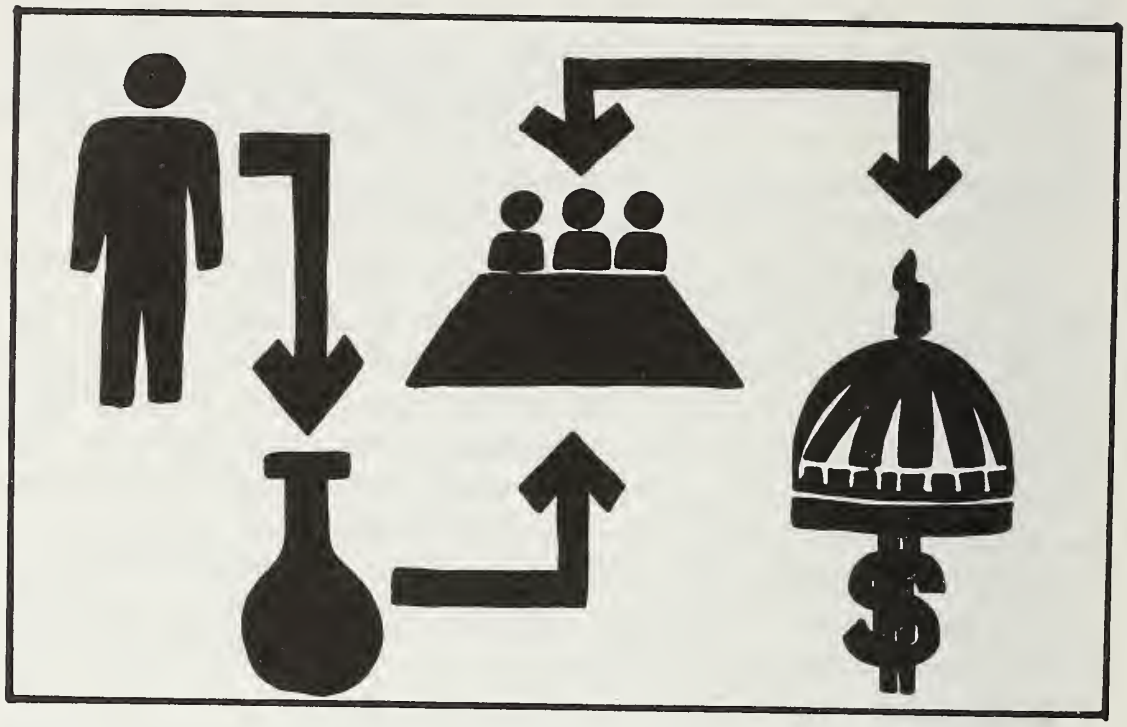
They may attend professional and scientific meetings. FDA and NIH have prepared written materials and conducted seminars and conferences on IRBs, which field investigators may attend as part of their continuing education process.[11] Experienced investigators sometimes give other investigators on-the-job training during routine inspections.

IRB inspections are initiated by the appropriate FDA office, coordinated by the Bioresearch Monitoring Office (to ensure that the inspection is timely and that the IRB is not inspected by more than one office, etc.), and sent to the agency's field offices for assignment to investigators. To schedule an inspection, a field investigator contacts one of the responsible individuals at the institution and arranges a mutually acceptable time. When the field investigator arrives at the institution, a formal "Notice of Inspection" form is shown to institutional officials to let them know that the investigator is a properly authorized.

In conducting an inspection, field investigators follow the *FDA Compliance Program Guidance Manual*, which describes the information sought and provides detailed guidance for determining the adequacy of the IRB's procedures. The investigator interviews appropriate persons in the institution to obtain a clear understanding and description of the IRB's policies and procedures. Using available documentation, the investigator also traces one or two studies through the review process: IRB procedures and membership are examined to see whether they conform to FDA regulations. The investigator obtains copies of records of IRB membership, IRB procedures and guidelines, minutes of meetings at which the studies were reviewed and discussed, material on the studies submitted by the clinical investigator to the IRB, and any other materials pertaining to these studies. On occasion, when invited and when it coincides with the inspection date, FDA field staff attend meetings of IRBs. However, such attendance has apparently been infrequent.

At the end of the inspection, the investigator conducts an "exit interview" with the responsible institutional representative(s) (unless the institution or IRB chairperson decides otherwise). The investigator reviews initial findings, describes any procedures that clearly deviate from current regulations,

[11] The FDA informed the Commission that in 1982 it held six training conferences of one and one-half days each around the country for field investigators specializing in the Bioresearch Monitoring Program. Field staff also attended eight regional conferences for IRBs cosponsored by NIH and FDA. Previously (in 1978-1979), more than half the field offices participated in full-day seminars on IRBs, during which the rationale behind the compliance program, the expected performance of IRBs, the evolution of protection of human subjects, and inspection procedures were covered.



and suggests corrective actions. During the discussion, institution officials frequently discuss their problems and plans for modifying their IRB's procedures.

After the inspection visit, the investigator prepares a written report with recommendations for action seen as necessary. This report includes a narrative description of the discussions that took place, the investigator's initial findings, and institutional responses and questions. Attached to the report are copies of the documents collected by the investigator during the inspection. This report is forwarded to FDA headquarters for detailed evaluation by scientific personnel in the FDA office that initiated the inspection.

Because headquarters personnel have reviewed the procedures of hundreds of different IRBs, they are able to compare the materials not only with the requirements of the FDA regulations, but also with commonly accepted committee practices. As a result, the institution may be offered advice on ways to streamline or improve the IRB's review procedures. The headquarters office, after reviewing the completed inspection report, makes a final classification evaluation—either no action indicated, voluntary action indicated, or official action indicated. There are three different levels of voluntary action category. The classification given to the report is used in determining the scheduling of the next inspection of the IRB.

When the headquarters has completed its evaluation, the institution is sent a letter that comments on good committee practices and that describes any deficiencies observed and corrective actions needed. Where major or important corrections are needed, the institution is required to provide a written response describing how and when they will act. At times a follow-up inspection may be conducted.

The stated objectives of FDA's inspection program are to document IRB compliance and to improve IRB performance by providing information and encouragement to institutions. The inspections are intended to compare the IRB's practices and procedures with the requirements of the current regulations and with standards of performance that are generally accepted by the IRB community. FDA states that the IRB inspections do not have the usual compliance/regulatory thrust of conventional FDA inspections; instead they are meant to be "advisory" in nature. It is also recognized, however, that sanctions might be invoked if serious or continuing deficiencies are encountered.

FDA estimates that each inspection involves an average of 28.1 field hours and 20 bureau hours. The total cost of FDA's IRB inspection program in FY 81 was approximately $399,168. In that year, FDA conducted 352 IRB inspections at an estimated cost of $1134 per inspection. The total cost includes salaries of field investigators and bureau personnel, the field costs of travel and per diem, and clerical and administrative overhead. Activities covered include preparation of the assignment, conduct of the inspection, preparation of the inspection report, agency review, preparation of correspondence, and follow-up.

The OPRR Approach. The NIH Office for Protection from Research Risks (OPRR) has several sources of information concerning IRB implementation of the HHS regulations. OPRR's primary source is the information each institution provides in its written assurance that it will comply with the regulations. The assurance provides OPRR with information concerning the IRB's composition and some of its procedures. The information contained in an assurance, however, provides only a picture of the IRB's *intention* to comply with certain formal standards. The assurance provides little information concerning the *actual* performance of the IRB. In the past, new assurances have been negotiated only when a major change in the rules has taken place, although IRBs are required to report changes in membership to OPRR.

A second source of information about IRB functioning comes to OPRR via activities of "scientific review groups," more commonly known as study sections. These are the peer review groups, organized by specialized areas of medical science, that advise the NIH on the scientific merit of applications for grants and proposals for contracts. Under current procedures, study sections are also responsible for evaluating the investigators' descriptions of six factors that summarize the protections for human subjects in the research. The "summary statement" prepared for each application by the study section's executive secretary notes any concerns raised by review group members about the adequacy of procedures for minimizing

risks and protecting subjects from harm. OPRR receives copies of such statements.[12]

In the past, OPRR had no automated system for detecting patterns linking particular IRBs to ethical questions raised by review groups. Any grouping of information from summary statements had to be done manually, and in many cases OPRR could not be certain, without a special inquiry, which of several IRBs at an institution had reviewed a proposal in question. Thus, OPRR had only limited ability to make full use of the study section's comments as a source of information about IRBs. However, at the Commission's September 1982 meeting, OPRR Director McCarthy reported that an automated data system was nearly ready; he subsequently advised Commission staff that the system would be fully operational by May 1983. It will enable OPRR to aggregate concerns about human subjects that are raised by study sections and to identify those IRBs that approve applications and proposals that are subsequently questioned at an unusually high rate. OPRR will know how many applications each IRB reviewed and approved in any given period and how many of those that were approved were the subject of ethical concerns in study section review. It will also know which concerns raised by a study section were regarded as so serious that funding was withheld.

It is important to recognize that, for several reasons, the raising of a concern about human subjects at the agency level does not necessarily identify a problem that was missed by an IRB. First, under present rules, IRB review may take place up to 60 days after submission of an application, and a study section may review an application before revisions required by the IRB have been incorporated. In these instances, criticisms of the proposal can hardly be taken as an indicator of IRB failure. Second, some concerns raised by study sections pertain to judgments about which reasonable reviewers can disagree. Finally, there is no reason to believe that judgments reached by study sections concerning the protection of human subjects are necessarily more sound than those reached by IRBs.

Indeed, because of differences in the purpose, composition, and procedures of the two types of bodies, it is to be expected that the IRB's judgments on at least some issues have a firmer base than do similar judgments made by study

[12] In the case of applications and proposals that are to be funded, the awarding unit is responsible for seeing that questions relating to the protection of human subjects are resolved prior to funding. In cases in which applications and proposals are not selected for funding, OPRR sends the IRB a letter explaining the study section's concerns relating to human subjects. The purpose of this letter is to inform the IRB of concerns raised by the study section, because the proposed activity may receive funding from sources other than HHS.

sections. IRBs have a diverse membership that is appointed to consider the protection of human subjects; study sections are primarily scientific review bodies whose members, usually from a single discipline, are chosen for their scientific expertise. Because study sections meet only three or four times per year, they may not always have time to do a careful and thoughtful review of ethical issues in addition to their evaluation of scientific merit. On the other hand, study sections often have expertise not possessed by the IRBs, particularly on matters pertaining to the risks and benefits associated with the proposed research. Given the differences in composition of the two types of bodies, HHS considers their judgments to be complementary rather than redundant.

The computerized system at OPRR will ensure that IRBs whose work is repeatedly questioned by study sections will come to the attention of OPRR for further evaluation. Such IRBs could be given priority for site visits or for other actions to encourage improvements in performance. On the whole, however, there is no reason to assume that ethical problems raised by a study section necessarily indicate some type of failure by the IRB; such problems must be interpreted with care.

OPRR has used a third approach to obtain information about the implementation of the HHS regulations. Although OPRR does not conduct periodic site visits to assess the adequacy of compliance with HHS regulations, it has conducted several different types of visits to institutions.[13]

Visits connected with official investigations of an institution's possible failure to comply with HHS regulations or with the provisions of its assurance of compliance. These formal visits usually follow a preliminary investigation by NIH and by the institution itself. Visitors may include OPRR and NIH personnel, as well as experts from outside the Federal government. Repeated or extended visits may be required. A visit involves not only interviews and reviews of documents pertaining to the matter under investigation but also a review of institutional policies and procedures for human subjects research, administrative arrangements and support for the IRB, and IRB records. After the investigation is complete a final report is prepared, and the institution and implicated individuals are given an opportunity for comment. The investigation may lead to specific recommendations for changes in institutional policies or procedures or to official actions in response to a determination of regulatory noncompliance. In the past year OPRR was involved in such visits to four institutions.

[13] This description of OPRR visits to institutions is based on a letter from Charles R. McCarthy, Director, OPRR, to Bradford H. Gray (Nov. 19, 1982).

Visits to assess the adequacy of institutional policies, procedures, and administrative arrangements for implementing institutional assurances with the HHS regulations. Such visits may be done at the invitation of the institution, when an institutional change occurs, or when questions arise during the grants review process about the adequacy of an IRB's work (although OPRR does not consider these visits to be "for cause"). Some such visits may take place to verify compliance with earlier modifications of institutional procedures or conditions imposed by OPRR. Thus, the visits may involve a prospective or retrospective determination of adequacy of compliance. Specific recommendations may be made either to the institution or to HHS. These visits may be done by one or two OPRR staff and may include outside experts. The visit includes interviews with appropriate officials, a review of relevant records and documents, and, where possible, participation in an IRB meeting. OPRR indicated to the Commission that their personnel made such visits to seven institutions in the past year.

Visits to provide technical assistance to institutions (officials, IRB members, researchers) in implementation and interpretation of HHS regulations. This usually involves consultation on specific matters needing clarification or the resolution of issues regarding a particular research activity; assessment of institutional provisions for protecting human subjects is at most a subordinate activity. OPRR personnel visited eight institutions for such purposes in the past year.

Incidental visits that occur when OPRR staff will be at or near an institution for some other purpose. Although such visits may be informal, they are usually planned so that arrangements can be made to meet with appropriate institutional officials. An incidential visit would involve a general review of the procedures and operations of the IRB and its staff and related administrative offices, an examination of relevant records, and, if the timing permits, attendance at an IRB meeting. Incidential visits provide an opportunity to discuss either general problems involved in the protection of human subjects or problems that are peculiar to the institution. OPRR indicates that such visits provide "a general impression of institutional arrangements for protection of human subjects, but no overall assessment is attempted." Such visits were conducted at four institutions in the past year.

Informal meetings with institutional officials and IRB members. These visits may also occur incidental to other OPRR business and are less for the purpose of making any assessments than for the purposes of advice, consultation, and professional exchange. Such visits were conducted at eight institutions in the past year.

OPRR (and FDA) also had opportunities to exchange views with officials and IRB members from more than 360 institutions in a series of nine NIH/FDA workshops on IRBs that were held around the country. In addition, OPPR staff made presentations or participated in panels in more than 20 other regional and national meetings of organizations conducting human subjects research.

Summary

The activities of FDA and OPRR provide examples of procedures used by Federal agencies to obtain information about the implementation of their rules to protect human subjects. (It should be noted that some other agencies also use such procedures; for example, both the Veterans Administration and the Federal Bureau of Prisons conduct systematic site visits to review IRB performance.[14]) Historically, OPRR has relied primarily on the information obtained in institutional assurances of compliance. Concerned about the limitations of such advance assurances of compliance, the National Commission for the Protection of Human Subjects in 1978 recommended that a program of peer-based site visits be undertaken. For the purpose of exploring the need for and feasibility of such site visits, this Commission undertook the site visit project described in Chapter Four.

The FDA clearly has a well-established program for inspecting IRBs. Although this program seems to meet FDA's regulatory needs, the inspections have been criticized for being excessively concerned with the paper indicators of regulatory compliance, and the FDA field staff has been criticized for being unfamiliar with the work of IRBs. The Commission is aware that the FDA has taken steps to improve the preparation of its field staff and that FDA tries to provide IRBs with information about "good committee practices" as well as regulatory violations. The Commission also notes that negative opinions of the FDA's program are far from universal among IRBs that have received inspection visits in recent years.

Nevertheless, the FDA inspections are quite different from site visits that use experienced IRB members as visitors and that are oriented toward the quality of performance. The Commission decided it was worth exploring this alternative approach. The Commission's site visit project was not undertaken as a criticism of an agency that has clearly made substantial efforts to meet its responsibilities; rather it was to explore the usefulness of a contrasting approach.

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[14] PROTECTING HUMAN SUBJECTS, *supra* note 1.

IRB Site Visits—An Exploratory Assessment of a Procedure for Evaluating IRB Performance

4

In addressing its mandate to report on the adequacy of implementation of Federal rules for protection of human subjects, the Commission recognized that its role was not to attempt to monitor the performance of IRBs. Rather, because of the limited information currently available, the Commission devoted its efforts toward improving the methods by which IRB performance can be both evaluated and improved.

Several sources of information about IRBs do exist, most notably in the institutional assurances of compliance and other materials on file with the HHS Office for Protection from Research Risks, in reports on FDA's IRB inspection program,[1] and in data compiled from a detailed survey of IRBs conducted under the auspices of the National Commission for the Protection of Human Subjects.[2] As a source of current information about the performance of IRBs in implementing the regulations, each of these has significant limitations.

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[1] Comptroller General of the United States, FEDERAL CONTROL OF NEW DRUG TESTING IS NOT ADEQUATELY PROTECTING HUMAN TEST SUBJECTS AND THE PUBLIC, U.S. General Accounting Office, Washington (1976); transcript of the FDA's IRB Compliance Activity Workshop, Nov. 7, 1980, at 11-26.

[2] Robert A. Cooke, Arnold S. Tannenbaum, and Bradford Gray, *A Survey of Institutional Review Boards and Research Involving Human Subjects*, in National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, APPENDIX, U.S. Government Printing Office, Washington (1978). The study is summarized in Chapter 2 of the National Commission's REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, U.S. Government Printing Office, Washington (1978) *See also* Bradford H. Gray, Robert A. Cooke, and Arnold S. Tannenbaum, *Research Involving Human Subjects*, 201 SCIENCE 1094 (1978).

As described in Chapter Three, OPRR's data consist largely of information about IRB members and institutional promises to comply with HHS regulations; and FDA's information, though pertaining to the implementation of FDA regulations, is largely concerned with regulatory compliance in a limited number of IRBs (those that review research regulated by FDA). The National Commission data are the most detailed available, but they are several years old and are more descriptive than evaluative.[3]

The National Commission's study demonstrated the difficulty of assessing IRB performance. Using data obtained through interviews and from an examination of consent forms, several measures of IRB performance were developed, including: (l) the comprehensiveness of IRB discussions, as reported by IRB members; (2) the frequency with which the IRB requires modifications in proposals and consent forms; (3) the readability and completeness of consent forms; (4) IRB members' evaluations of the IRB's performance; and (5) research investigators' evaluations of the IRB's performance. Clearly, all these measures have weaknesses and none is comprehensive; however, each pertains to an important aspect of IRB performance. Furthermore, among the 61 IRBs studied, there were large differences in performance on all the measures. For example, some IRBs had modified every proposal they had reviewed, while other IRBs had modified none. Since detailed data were collected about the composition and procedures of IRBs, it was possible to study the relationship between such factors and the performance of IRBs.

Although IRBs varied considerably in their membership and review procedures, a statistical analysis did not show that IRB procedures or composition per se made any difference in performance. Furthermore, IRBs that ranked high on one measure of performance did not necessarily score high on other measures; the various measures were largely independent of each other.

One possible explanation for the lack of a statistical relationship between IRB composition or procedures and performance is that an IRB's performance is a function of its particular combination of many different factors. These might include the type of institution it serves, the amount and types of research it reviews, the size and diversity of the membership, a wide assortment of procedural variations, the frequency and length of meetings, the leadership provided by the chairperson, the expertise (and personalities) of the various members, and so forth. No single combination of these and

[3] Cooke, Tannenbaum, and Gray, *supra* note 2. The study covered research reviewed by IRBs between July 1, 1974 and June 30, 1975, after the initial HEW regulations for protection of human subjects became effective.

other factors seems likely to be the sole key to IRB success. Given this, it is impossible to tell how well an IRB is performing by examining a list of its members or a description of its review procedures, although such information may suggest that certain problems might be present.

Many aspects of the procedures necessary to fulfill the intention of the regulations are not explicitly specified either in the regulations or in the institutional assurances of compliance. This accounts for the wide variation among institutions in the way that they have chosen to implement the regulations.[4] The flexibility that is permitted is appropriate in light of the differences among the institutions, especially since little is known about the relationship between an IRB's composition and procedures and its effectiveness in protecting human subjects. The wide latitude that is given institutions under the regulations, however, may mean that simple compliance with the regulations may not assure adequate protection of human subjects.

Satisfactory implementation of the rules—particularly, the spirit of the rules—may go beyond mere regulatory compliance. This may account for the finding in the National Commission's study that among the IRBs examined (all of which had provided HEW with satisfactory assurances of regulatory compliance), there were substantial differences on every measure of performance.[5] It may also partially explain more recent findings of wide differences among IRBs in their responses to identical proposals,[6] and anecdotal reports of

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[4] *Id.*

[5] *Id.*

[6] Jerry Goldman and Martin Katz, *Inconsistency and Institutional Review Boards*, 248 J.A.M.A. 197 (1982). As Robert Veatch notes in an accompanying editorial, consistency would not prove that IRBs make "correct" choices. Nor is complete consistency a reasonable goal in a system that is decentralized and in which there is no systematic reporting of IRB decisions, no hierarchical appeals process, and thus, no method of applying to IRBs any precedents that may have been established by other IRBs. Robert M. Veatch, *Problems with Institutional Review Board Inconsistency*, 248 J.A.M.A. 179 (1982) In its comprehensive review of the IRB system, the National Commission concluded that the advantages of a decentralized IRB system far outweigh the advantages of a more centralized system; the Commission also declined to recommend establishment of a formal appeals system that would allow a local IRB's decision to be overruled. REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, *supra* note 2. It should be noted in this regard that Federal agencies may override IRB approval and decline on ethical grounds to support a project that has been approved by an IRB. This is not an appeals process, however, since the agencies may not fund a project that has been disapproved by an IRB; nor does it provide a system of precedents. The National Commission did urge that better means of communication among IRBs be developed. This has occurred through meetings sponsored by

IRBs imposing seemingly arbitrary and idiosyncratic conditions on some research projects.[7]

The National Commission concluded that a full assessment of an IRB should be based on an examination of that IRB's performance in its particular institutional context and with its particular work load, membership, and procedures. Therefore, the National Commission recommended in 1978 that Federal compliance activities should include routine site visits and audits of IRBs.[8] This recommendation has never been implemented, however, and although the FDA inspection program shows that some types of regulatory noncompliance by IRBs can be documented, the usefulness of site visits for a more general and qualitative assessment of an IRB's implementation of the intention or spirit of the regulations—and for improving the review process—has remained hypothetical.

After consultation with a group of advisors in 1981, the President's Commission decided to explore the possible benefits of sending individuals experienced in the work of IRBs on site visits. It was believed that such site visitors could assess the qualitative aspects of the functioning of IRBs, particularly if the visits were collegial and more educational in orientation than is typical of inspections or investigations. The Commission directed its staff to conduct a small-scale study to determine the usefulness of such site visits as a method of both evaluating the IRBs' implementation of the regulations and improving their functioning. In addition, the study was to suggest criteria for judging IRB performance.

The question of the usefulness of site visits involves several subsidiary questions. What can be learned by conducting site visits? Is it possible to tell if an IRB is doing a good job? What factors reveal this? Are these factors accessible through means other than site visits (*e.g.*, reporting requirements, record review)? What are the limitations on what can be learned through site visits? Is there significant margin for improving IRBs? Can site visitors make useful suggestions in this regard?

OPRR, FDA, and others, and through the development of a journal, IRB, published by the Hastings Center. However, none of this is to say that the amount of variation found in the Goldman and Katz study is either desirable or necessary. Their study clearly suggests that some IRBs make better decisions than others, a problem for which the existing system makes no provisions.

[7] Complaints about IRB decisions are frequently heard at IRB conferences but such complaints are not necessarily well founded. Summaries of the testimony received at its IRB hearings are published in REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, APPENDIX, *supra* note 2.

[8] REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, *supra* note 2, at 10.

In addition to exploring the usefulness of site visits, the Commission's project was intended to explore how to conduct site visits. What constitutes a workable, useful site visit? What elements are essential? For example, must site visitors attend IRB meetings to assess an IRB's performance?

The goal of the project was not to demonstrate that one particular way of conducting site visits is best; in fact, several formats were tried. The first site visits were undertaken with what seemed to the site visitors and institutions to be a reasonable approach, and on subsequent visits modifications and additions were made as seemed warranted. Thus, although the basic concept of a peer-based educational site visit was constant, the details of the site visit process evolved as experience was gained.

Methods

The Sample. Between October 1981 and June 1982, site visit teams organized by Bradford Gray, special consultant to the Commission, conducted visits to 12 IRBs at 10 institutions. (At each of 2 institutions, 2 IRBs were visited.) Seven of the IRBs were located in medical schools; of these, two were also responsible for reviewing nonmedical research for the university of which the medical school was a part. Two IRBs were for nonmedical research at universities that had a separate IRB for the institution's medical school. Three IRBs were at more specialized medical institutions—a hospital for children, a hospital for treatment of cancer, and an institution for the training and treatment of handicapped children. East Coast, West Coast, and Midwestern institutions were included among those site-visited; site visitors were recruited from those same areas.

No claim of representativeness is made for the institutions that participated in the site visits. They were selected for diversity, feasibility of scheduling, and geographic accessibility for site visitors.

The Site Visitors. The Commission's site visits were conducted by teams that consisted of two experienced IRB members who were biomedical or behavioral scientists, one person who had carried administrative responsibility for an IRB, and the Commission's special consultant on this project. It was felt that the teams should consist of at least three persons to reduce the possibility that personal idiosyncrasies of reviewers could play an unduly prominent role. Most of the IRB members were the chairpersons of their IRB. All of the site visitors had an ongoing interest in IRBs and the issues with which they deal.[9]

[9] The following individuals acted as site visitors: Nini Almy, Ph.D., University of Illinois; Nancy Azarian, Children's Hospital Medical

Arranging the Site Visits. Many of the site visits were arranged in pairs on consecutive days. This lowered costs and enabled each site visitor to conduct two visits. These visits were generally scheduled to allow visitors to attend the meeting of one of the IRBs. Since one initial question about the site visits was whether attendance at an IRB meeting was necessary, the fact that most site visitors were able to participate in two site visits, only one of which included attendance at a meeting, was important to the design of the site visit project. The disadvantage of scheduling visits on consecutive days was that it extended the time commitment required of site visitors, thereby reducing the pool of persons who were available to conduct site visits on any given dates.

The same basic process was followed in arranging all site visits. The Commission's consultant contacted the institution by telephoning the person registered with the HHS Office for Protection from Research Risks (OPRR) as either the official contact person at the institution or the chairperson of the IRB. The purpose of the requested visit was explained, including the relevance of the site visit project to the Commission's mandate, and a request for cooperation was made. Assurances were given that no evaluations of identified institutions would be made in any Commission meeting or publication and that no reports would be made to any government agencies. A request was made that the visitors be allowed to attend a meeting of the IRB, if possible, and to meet with a diverse assortment of IRB members, institutional officials, and investigators.[10] Access to IRB minutes and IRB files on several projects, selected for diversity, was also requested. The process of scheduling the people with whom the Commission visitors met was left in the hands of the institution.

Institutions varied in their orientation to the site visit. Some appeared to welcome the opportunity to share their experience and obtain feedback from the site visitors and

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Center, Boston; Bernard Barber, Ph.D., Columbia University; Sanford Chodish, M.D., Boston City Hospital; Jeffrey M. Cohen, Ph.D., SUNY, Albany; Dale Cowan, M.D., St. Luke's Hospital, Cleveland; Norman Fost, M.D., University of Wisconsin School of Medicine; Erica Heath, University of California School of Medicine, San Francisco; Norman Kahn, Ph.D., Columbia University School of Physicians and Surgeons; Robert Levine, M.D., Yale University School of Medicine; James Lipsky, M.D., Johns Hopkins University School of Medicine; Harry B. Neustein, M.D., Children's Hospital of Los Angeles, Alvin Parrish, M.D., George Washington University Medicial School; Beverly Penrose, St. Louis University Medical Center; Marcia Pines, Johns Hopkins School of Hygiene and Public Health; John F. Schacher, Ph.D., University of California Los Angeles.

[10] No attempt was made to meet with research subjects on these site visits because of time constraints, logistical difficulties, privacy concerns, and anticipated problems of interpretation.

seemed to be very relaxed and open, even about their shortcomings. Other institutions were more apprehensive about the site visit and guarded in their response to it. In all cases, it was stressed that participation was voluntary. No institution refused to participate in the site visit project, although scheduling difficulties precluded the participation of some institutions.

Conducting the Site Visits. For most of the site visits, the visitors were sent some information about the institution in advance, including the composition and policies of the IRB. Some institutions provided this information in the form of the institution's written assurance of compliance with HHS regulations. At several institutions where the site visitors attended an IRB meeting, they were given advance copies of the research proposals that were scheduled for review. This gave the site visitors a more informed perspective from which to observe a meeting.

The Commission's site visits generally lasted one day. (Early in the project, two IRBs at a single institution were visited in one day. The site visitors involved concluded that more than half a day would generally be needed to conduct an adequate site visit, and thereafter one-day visits were the rule.) It should be recognized that a one-day site visit is necessarily of limited depth. Clearly, some visits could consume several days if the visits were intended as a full review of the IRB's compliance with the regulations and careful documentation of its performance.

A typical site visit began with a meeting with the chairperson of the IRB and other institutional officials who provided information about the institution, the IRB, and its review procedures. During the day, the site visitors met with an assortment of IRB members and investigators, either individually or in groups. A valuable source of information at some institutions was the person who performed administrative functions for the IRB. The meetings generally lasted 20-30 minutes. The time spent per person was reduced when meetings were held with groups, since there was less repetition of points already covered.

During each site visit, some time was spent reviewing the IRB's records. In some visits, a block of time—usually about a half-hour—was devoted to the records; on other visits, records were available for review while other activities, such as interviews, were taking place. The regulations require that minutes show the basis for any changes in research required by the IRB and summarize IRB discussions of "controverted issues and their resolution." In some cases, site visitors were able to learn a great deal about the issues raised by the IRB from a review of the minutes. In other cases, site visitors learned only that the minutes were uninformative, either

because they consisted of little more than a list of projects that had been approved or because much of the IRB's activity took place outside of meetings (*e.g.*, in the activities of primary reviewers who negotiated changes with researchers prior to the review of the project at an IRB meeting).

The site visitors usually examined the files of several research projects, generally selected at random, that had been previously reviewed by the IRB. Since project files generally contain information about proposed research and the IRB's reactions (in the form of correspondence or notes about telephone conversations with the investigator), these project files helped to construct a picture of an IRB's functioning.

Site visitors did not attempt to ascertain whether all (or even a representative sample) of approved consent forms adequately disclosed the purpose and risks of the research and were in reasonably understandable language. Rather, by considering the IRB's composition and its procedures for handling consent, discussing the IRB's work with investigators and IRB members, and examining several consent forms, the site visitors tried to make a general judgment about whether the IRB was knowledgeable about, and was giving adequate attention to, the matter of informed consent.

During the site visits, the visitors generally stayed together. This was done in part to develop information about the extent to which a set of site visitors from *different* IRBs would reach similar assessments based upon exposure to the *same* information. If site visitors who had the same basic experience at an institution were to reach divergent conclusions about the adequacy of the performance of an IRB, that would raise certain concerns about the site visit procedure. If, on the other hand, site visitors were to reach divergent conclusions after exposure to *different* individuals or experiences on the site visit, no answers could be given to questions about whether

site visitors are reasonably objective, whether they apply similar standards, and whether their judgments are reliable. In some cases, not all site visitors reviewed the same records; but interviews with IRB members and investigators were generally conducted by the site visit team as a group.

The final source of information for site visitors was attendance at the meetings of six IRBs. Although most of the institutions that were visited were quite willing to invite the site visitors to their meeting, one institution refused to allow them to attend (although the site visit took place on the same day that the IRB met) on the basis of an opinion from its legal counsel that it did not have to allow the site visitors into the meeting. (This was a regrettable misunderstanding of the request to attend, since no suggestion had been made that the institution had to allow the site visitors into the meeting.)

Post-Visit Assessment. At the end of each site visit, the visitors were asked to make a series of judgments about the IRB visited. They were asked to identify the major strengths and weaknesses of the IRB and to respond to 16 specific questions about the quality of the IRB (see Appendix H, pp. xx *infra*).

Site visitors were asked to provide their assessments about these matters in writing. Because the site visitors' responses did not always clearly reveal whether their view was positive or negative, beginning with the fourth IRB, site visitors were asked to place their response to each question on positive to negative scales, in addition to providing a written explanation of their views.

Following ten site visits, members of the team made their assessments independently of one another. This provided a basis for examining the degree of agreement among the visitors and the basis of their judgments. After two site visits, the team met as a group to develop a consensual evaluation.

Site visitors were also asked to evaluate the site visits themselves by responding to nine open-ended questions about such things as their ability to make a firm assessment of the IRB(s), the usefulness of the site visits as an educational device, the importance of attending an IRB meeting, the amount of time that should be devoted to site visits, and how the time should be allocated (see Appendix H *infra*).

Following several site visits the institution was sent a letter summarizing the site visitors' views. This was not done after the first few site visits, since it was not then known whether site visitors would be able to agree on any useful conclusions. However, after it had become apparent that site visitors could indeed agree about what they had seen and that their judgments might be of interest and use to institutions, efforts were made to summarize the site visitors' conclusions in a letter. Drafting letters to the institutions was more

complicated when the site visitors' judgments were not pooled before they returned home. In such cases, the site visitors' individual evaluations were collected and integrated by the Commission staff; then a letter was drafted and circulated among the site visitors, and necessary revisions were made before the letter was sent to the institutions. The institutions were encouraged to respond with their own assessment of the site visit in terms of both the burden that it presented and its usefulness to the institution. Most did not do so.

Findings

The two major questions to which the site visits suggest answers are: (1) Is there significant room for improvement in IRBs? and (2) Are site visits useful for evaluating IRB performance?

Among the questions answered by visitors after each site visit were three general, open-ended questions (see Appendix H, pp. xx infra) regarding an overall assessment of the IRB, identification of the IRB's major strengths, and identification of its major weaknesses. Answers to these questions reveal the extent of general agreement among the site visitors and illuminate the dimensions of IRB performance that were most striking to site visitors.

The site visitors' responses to 16 more specific questions provide a basis for assessing the extent to which site visitors were able to judge different aspects of an IRB's activities, the extent of agreement among site visitors, and how these matters varied from topic to topic and from site visit to site visit. These responses provide some information about those dimensions of an IRB's operation that can be assessed through site visits, the degree of consistency among site visitors, the nature and extent of variation among IRBs, and the extent to which IRBs that are strong in one dimension are strong in others.

The Performance of IRBs. Great variations were seen among institutions in the degree to which they have developed a strong and effective IRB. The sample of IRBs visited was small and, though several different types of institution were included, was not selected in a way that would allow statistical generalizations to be made. Nevertheless, this group of IRBs showed great differences in the effectiveness with which the Federal rules for protecting human subjects have been implemented.

Of the dozen IRBs visited in this project, the following very general characterizations of the site visitors' conclusions can be made.

At three of the IRBs, site visitors had no serious concerns and had no major suggestions for improvement, though a number of minor suggestions and observations were made. For

example, at one of these institutions, where the site visit included attendance at the IRB meeting, the following summary comments were made by the four site visitors:

> By observation, this appears to be a very effective, well organized, highly participatory IRB. It shows a good range of concerns. It has a problem-solving orientation. A knowledgeable and well respected chairman. Stable, diverse membership that has a good mixture of concerns and expertise.
>
> This is a well constituted IRB. The chairman, who has served for many years, is very conscientious. He devotes at least one full day per week to committee activities. The Associate Dean for Research provides initial review of all research proposals before they are forwarded to the IRB. The committee appears to maintain open communication with the investigators. Secretarial staff and space for the committee files are provided by the administration.
>
> I had a very good feeling about this IRB in that I thought that its members had a clear idea of what the function of an IRB should be, that they exercised their responsibilities knowledgeably, effectively, and that they consequently did an excellent job in protecting human subjects.
>
> An excellent medical review committee, with a strong, committed, effective chairman. The actual meeting we attended was fully attended (20 or so people), all of whom seem to be well prepared and who participated well. 'Laymen' as well as experts were evaluating technical material and seemed fully able to do so. The committee is especially helpful in the matters of informed consent and risk/benefit ratio.

The only critical comments regarding this particular IRB were that its membership would be strengthened by the addition of a statistician and that the chairman could benefit from some additional staff support.

A number of ingredients appeared to the visitors to underlie the success of this IRB, which was located in a university medical center. The membership was experienced, stable, and quite diverse, including not only biomedical researchers but also senior people from nursing, social work, philosophy, religion, and the behavorial sciences. Under this IRB's procedures, all members of the committee received copies of all proposals, a primary and secondary reviewer was assigned for each proposal, and the primary reviewer presented a brief description and evaluation of the proposal during the IRB meeting. The primary reviewers were assigned in sequence, not on the basis of expertise. This system appeared to enhance the involvement and, over time, the expertise of all

members of the IRB. It may also have contributed to the free and open discussion that the site visitors observed during the IRB meeting.

Two other IRBs, one of which was also located in a university medical center and the other of which was a university IRB that dealt only with the social and behavioral sciences, were seen by the site visitors as strong IRBs without serious problems. (In neither of these cases, however, did site visits include attendance at the IRB meeting.) The common factors in these IRBs were the competence and commitment of the members (which was apparent in conversations) and the thoroughness of the procedures.

Five of the IRBs were seen by site visitors as reasonably effective and competent but as having procedural problems that limited some aspect of their functioning. The following excerpts from site visitors' comments show the mixture of strengths and weaknesses of these five IRBs.

> This IRB has a firm grasp on its responsibilities and has designed procedures suitable for the institution that effectively discharge these responsibilities. It views its role as going beyond merely satisfying the DHHS regulations. It views itself as having an educative function in that it works with investigators in developing sensitivity to ethical issues and arriving at suitable mechanisms for pursuing ethical research that maximally safeguards subjects of research. The major strengths of this IRB are (1) its chairman, who is extremely knowledgeable about the ethical issues that attend human research and is sensitive to the balance of issues in not defeating good research and in safeguarding the safety and welfare of the subjects, and (2) the subcommittee, which reviews the scientific aspects of proposed research. One of the major strengths may at the same time be a major weakness. It appears that the real action of the IRB's activities takes place in the subcommittee [which reviewed proposals prior to the IRB's meeting and made recommendations to the IRB] since this is where the nitty-gritty issues of the research appear to be reviewed. Because the scientific expertise on the full committee appears to be somewhat limited, there appears to be a tendency for the full committee to more-or-less accept the recommendations of the subcommittee.
>
> This IRB appears to be fulfilling its obligations reasonably well. I felt that there was a clear intent to carry out their responsibilities in the protection of their human subjects. The major weaknesses of their IRB are that although the members receive a summary of the projects and have the full protocols available, only the two primary reviewers receive the full protocol. A second

problem is that heavy reliance is placed on outside reviewers who submit written reports and who in many cases don't attend the meetings.

This IRB appears to be functioning quite well despite the excessive reliance on paper. I believe there is room for improvement to: (a) speed up the process, (b) filter the reviewer comments and (c) provide more discussion and thus build a more 'communal ethic' and standard. Given their procedures, they do a good job. The major strengths of the IRB are its superb documentation and good involvement of all members and the allocation of responsibility. The major weakness of the IRB is a failure to allow opportunity for the generation of discussion because of excessive reliance on the efforts of individual reviewers.

My overall assessment of the IRB was favorable and could be stronger if I knew that the subcommittees were functioning in a proper way. The major strengths of this IRB are the administrative support and the personal input by the administration. It is impressive to have a statistical office providing support to the IRB. The overall tone set by the Dean is very commendable. The major weakness appears to be the lack of detailed recordkeeping of the specific discussions (in subcommittees) that involve protocols. Another weakness was the lack of adequate information supplied to the non-subcommittee members of the IRB. This may lead to a particular problem for lay members.

This IRB functions at a rather minimal level, but reviews little research, which is mostly low risk social and behavioral research. It reviews only sponsored research, and the dean thinks that this is what DHHS intends. The chairman does little more than chair the meeting. The major strengths of the IRB are its stable membership of responsible people, and a strong non-institutional member. There is evidence of concern about the right things. The IRB seems to do what it is supposed to do, but probably little more. Nothing about this IRB is very elaborate or detailed, but that may be appropriate to the amount and type of research reviewed. There is little administrative interest in the IRB function, and probably little interest from committee members as well.

The site visitors had serious reservations about the commitment or effectiveness of the remaining four IRBs. The following comments indicate the nature of the problems that were identified.

In general, this is a good group of people. They could certainly use some advice on improving their efficiency. They could also use some education about the current

status of ethics and regulations in the field. They seem to do a particularly good review of scientific design and risk/benefit issues. However, they seem relatively inattentive to matters of assent, privacy, and confidentiality. The people on this committee are, in general, senior and highly respected members of the local staff and community. This gives them a good deal of authority. Their special reviewer system seems to assure a high quality of review of scientific design and risk/benefit issues. However, there is a general unfamiliarity with current regulations and the state of the art in ethical considerations. Apparently, they make very little effort to educate themselves and each other in this regard. They are also very inefficient. Expedited review procedures seem to consume as much time at convened meetings as do regular protocols. There is an excessive preoccupation with procedure, Robert's Rules-of-Order, formal motions, and so on. This does not seem to permit much free discussion of substantive issues.

This IRB appears to be highly organized for the expeditious review of protocols with two committees, each meeting monthly, and an overall executive committee. I was not impressed that much time was given to good review of protocols, and I think that there is a possibility that both the subject and the investigator could get shortchanged. The major strengths of this IRB are that most of the committee members seem to be well-motivated and sincere. There is an attempt to handle a large volume of work in as fast a time as possible. The major weaknesses are that the very efficiency that is apparent in the fast turnaround of projects seems to assure that each project gets little attention. In addition, there are only two reviewers, chosen for their knowledge of the subject, who get the protocol. The rest of the committee does not see them until the meeting (if then). The decision therefore seems to be made by only these two.

My overall concern is that the IRB is not adequately addressing, with full discussion and resolution of issues, scientific merit and informed consent. The major strengths of the IRB are its secretarial support and organizational aspects. However, the IRB does not have a full and complete discussion of the scientific merit as well as the nature of informed consent of protocols. It appears that once protocols are brought up for discussion, it is a foregone conclusion that they will be approved.

This appears to be a highly committed IRB that has adequate concern for the rights and welfare of human subjects. However, because of several characteristics of

> its functioning, it does its work at great cost to the institution and to investigators. These factors include a degree of indecisiveness, a tendency to give too much importance to minor matters, and procedures that do not make for efficient operation and which are difficult for investigators. While the IRB is very aware of the vulnerability of the subjects that are involved in the research, it does not appear to be operating with a sharp and clear sense of what it is supposed to be doing, perhaps signaling a lack of effective leadership.

These comments from site visitors' evaluations have been quoted at some length to illustrate the sharp differences in their reactions to various IRBs and the types of issues that were mentioned in their summary comments. While there was often variation among site visitors' assessments, at only one IRB did a site visitor disagree with the others about whether an IRB was generally doing a good job.

Factors Identified by Site Visitors in Discussing Strengths and Weaknesses of IRBs. Forty-two overall assessments (40 individual and 2 group assessments) were made by site visitors following the 12 site visits. In developing their overall assessments, site visitors commented on many aspects of IRB performance. These comments fall into eight general categories.

IRB composition. The composition of the IRB was one of the most frequently mentioned topics in the summary comments of the site visitors, appearing in the evaluations for 11 of the 12 site visits. Positive comments were made about some aspect of the membership of 9 IRBs, while some weaknesses were seen on 8 IRBs.

In most cases these comments pertained to the overall makeup of the IRB, although some comments pertained to the characteristics of particular members (*e.g.*, a strong non-institutional member). Among the membership characteristics mentioned favorably were the expertise, knowledge, and capability of the members, their authority and ability to command respect, their commitment and dedication, the range of issues that the membership was capable of addressing, the rapport among the members, and the diversity and stability of membership.

Among the negative comments of site visitors were suggestions that several IRBs would benefit from the addition of a particular type of member (*e.g.*, a statistician, a pharmacologist, racial minorities, or better community representatives). In other cases, the negative comments pertained more to the overall makeup of the IRB (its domination by biomedical scientists, the need for more diversity, the need for more senior, authoritative figures, or for persons more willing to be assertive in evaluating proposals).

IRB chairpersons. The summary comments for nine of the site visits included comments (both positive and negative) about IRB chairpersons. In six instances there were positive comments, noting that the chairman was devoted, knowledgeable, respected, or a good leader. The negative comments also pertained to six IRBs, but were more diverse. In three instances, at least one site visitor found the chairman exerting too much authority and control over the IRB. In two other instances, the site visitors felt that the chairman did not exercise enough authority, particularly in the meetings.

Institutional and administrative support. Site visitors' summary comments for ten visits included references to the support provided to the IRB. In nine instances there were positive comments about such factors as the capability of the staff, the clear commitment of the institution to the functions of the IRB (as indicated by such factors as financial support), and the degree of apparent familiarity with the activities of the IRB on the part of high institutional officials. Negative comments were made about the institutional support of five IRBs. These comments included the need for more staff support, the inappropriately large influence held by administrative officials or IRB staff persons, and a sense of minimal institutional commitment to the activities of the IRB.

IRB procedures. Site visitors' comments after all site visits included references to the IRB procedures. In ten instances there were positive comments about the procedures. Most of these were rather unspecific (*e.g.*, that the committee was well organized, had "good" procedures, had thorough procedures). A few comments about procedures pertained to more specific matters (*e.g.*, how the assignment of proposals to primary reviewers in sequence involved the lay members with a full range of issues, the quality of the materials given to members for review, the system of paper work that had been developed, and the quality of the screening process before proposals were circulated to IRB members).

Negative comments were made about the procedures of nine IRBs. Since these included some of the site visitors' most serious concerns, they are described here in some detail.

A significant procedural problem in six of the IRBs was the delegation of all or part of the review function. Two of the IRBs used scientific subcommittees to review proposals and make recommendations to the IRB. While all members of these IRBs could in principle raise questions about any issue, in practice one of the IRBs confined its attention almost exclusively to the issue of informed consent while the other discussed only an occasional issue on an occasional proposal. (It should be noted that in neither of these cases were the site visitors seriously concerned that the rights and welfare of the subjects were in

jeopardy. The concern was that the review process took place outside of the IRB meetings.)

Another way of delegating the review function was seen in an IRB that assigned proposals to a majority of IRB members for their individual review, transmitted the individual reviewers' concerns and comments verbatim to the investigator for response, and continued this process until the individual reviewers were all satisfied. At that point, a majority of the IRB members would have indicated their approval of the protocol, although no other IRB members had seen it; moreover, the IRB members who had seen it had not discussed it with each other and the proposal had not been considered in an IRB meeting. IRB members indicated to the site visitors that proposals were actually discussed in an IRB meeting only in the rare instance in which an issue was not resolved by the process described above. Formal approval of proposals did take place in IRB meetings, however. These procedures enabled the IRB, which reviewed several hundred new proposals per year, to meet only once a month for an hour or so for lunch. Nevertheless, the site visitors felt that the proposals were getting close and careful attention from competent IRB members. Their major reservations were that: (1) since investigators had to respond to the questions and comments of each IRB member, without benefit of group discussion, investigators must perceive this IRB as very idiosyncratic and inconsistent; (2) IRB members have only a minimal opportunity to learn from each other; and (3) issues that might have arisen in an IRB discussion had little chance to arise.

A third method by which the essential review process was delegated and took place outside of IRB meetings occurred at three institutions that assigned proposals to primary reviewers for their review and recommendation and did not provide other members of the IRB with copies of the proposals. Although the site visitors did not attend the meeting of these IRBs, it seems unlikely that effective discussion was possible.

A second procedural problem, which was seen at two institutions, was the use of primary reviewers who were not members of the IRB and who did not attend the meeting. The apparent consequence of this procedure was that the reviewers' comments often did not focus the IRB's discussion on ethical issues, presumably because the reviewer was not a member of the IRB, had little experience with its functions, and consequently introduced extraneous and poorly focused issues into the committee discussion. In both instances, the intent was to assign the proposal to reviewers who would be expert in reviewing the science in question. The effect, however, appeared in both cases to be detrimental to the IRB's discussions.

A third procedural problem, seen at only one institution, was the presence of the investigator during the IRB's entire

substantive discussion of the proposal. In the view of all of the site visitors who attended the IRB's meeting, there was a singular lack of open and free discussion in this IRB, which was concerned enough about the possibility of retribution against IRB members to use a secret ballot for committee votes.

Another procedural problem, seen at only one institution, was a lack of a common understanding among IRB members regarding their voting procedures. At least one member of the IRB told site visitors after the meeting that a proposal had been turned down because two members had voted against it, while the chairman indicated later that the committee followed majority rule and the proposal had accordingly passed.

A final set of procedural problems concerned paper work. Problems of this sort ranged from an almost total reliance on paper review with little or no substantive discussion, at one extreme, to the use of a subcommittee system for which no written records were kept, at the other extreme. In several other instances, minutes were so brief as to produce no record of substantive discussion at IRB meetings.

Sense of purpose and commitment. Less tangible than methods or procedures, but of equal concern to the site visitors, was the sense of purpose and commitment that was obvious at some IRBs and not apparent at others. This topic was mentioned in the summary evaluations of at least one site visitor at every IRB. At ten of the site visits, positive comments were made. These comments included such matters as the IRB's conscientiousness, complying with or going beyond the regulations, taking its responsibilities seriously, having a clear intent to be responsible, and having members who were interested, active, committed, or dedicated.

Negative comments were made after nine of the visits. (Site visitors showed considerable ambivalence on this matter, making both positive and negative comments in seven site visits.) The negative comments concerned a much wider variety of topics than the positive comments did. Site visitors at several of the institutions commented on such matters as ambivalence among members about the function of the IRB, the lack of a serious interest or intellectual commitment to the issues, and a failure to focus on the real ethical issues. Another dimension commented upon at two institutions was the IRB's lack of clear sense of what it was supposed to be doing. Other comments concerned the narrowness with which some IRBs had defined their role. At three IRBs, site visitors felt that much too little time was being devoted to the IRB function. If site visitors were in general agreement that an IRB was functioning without a clear sense of purpose and commitment (as was clear to site visitors in three cases), this cast doubt upon the overall effectiveness of the IRB.

Quality of discussions and decisions. Site visitors were able to obtain a sense of the quality of an IRB's deliberations firsthand at the six IRBs whose meetings they attended. For the other IRBs, judgments had to be made on the less satisfactory basis of discussions with IRB members and review of written materials such as minutes and correspondence. Thus, in many instances, site visitors' comments were based upon their having seen whether the IRB was addressing various types of issues (*e.g.*, risk/benefit, informed consent, design, or the particular vulnerability of a subject population). In other instances site visitors' impressions about the quality of discussions or decisions had a more tenuous base—such as an IRB's seeming focus on written documentation rather than the substance of informed consent,[11] and comments of IRB members that research design issues were not their responsibility, regardless of the effect on the risk/benefit question.

Of more general concern to site visitors were indications of the quality of the IRB's discussions and the apparent sensitivity of members to the finer points of the issues with which they dealt. Site visitors had comments about these matters at ten IRBs. In three of these cases, there were only positive comments; in four, there were only negative comments; and in the other three, there were both positive and negative comments. The positive comments pertained to such matters as the range of issues with which the IRB was concerned, the sensitivity and sophistication about ethical issues that were in evidence, the ability of the committee to focus on the serious issues while ignoring trivia, and the willingness of the committee to face and resolve issues. The negative comments were substantially mirror images of these positive comments. Thus, they pertained to a lack of awareness and sophistication about ethical issues evidenced in poorly focused meetings of some IRBs that led to indecisiveness, a lack of frank discussion, the effective freezing out of some points of view by dominant (usually senior biomedical) members of the IRB, and the lack of the sort of discussion about issues that would produce—over time—shared understandings among the members.

Since the IRBs that were visited varied widely in the extent to which substantive work took place in convened meetings (rather than in subcommittees or among individual reviewers), site visits varied in the extent to which attendance at a meeting gave an adequate picture of the IRB's work. A further limitation of attendance at IRB meetings was the unknown extent to which the presence of the visitors affected the meeting. It seems likely that if an IRB can perform well

[11] Several IRBs required signed consent forms for every research project under review, despite the fact that reasonable exemptions to written consent requirements exist under current regulations.

with site visitors present, it has performed well before, since it would be difficult to raise the relevant issues when they have not previously been raised. On the other hand, one IRB spent most of its meeting dealing with trivial issues and had difficulty resolving the issues that members raised; it is difficult to know the extent to which this was typical for that IRB rather than the result of the presence of visitors. Clearly, attendance at a meeting will not answer all questions, and it must be remembered that erroneous impressions can be created.

Approach taken by the IRB. Five site visits produced comments about the quality of the approach taken by the IRB. Most of these comments were favorable and pertained to the ability of the IRB to communicate and work constructively with investigators and to approach their responsibilities with an educational and problem-solving orientation. The main negative feature, mentioned after only one site visit, was a tendency to nitpick.

Efficiency. The final topic on which site visitors commented was the efficiency with which the IRB operated. Comments after five of the site visits included an observation that the IRB was operating efficiently and was well organized for meeting its work load, and comments after five other site visits included observations about the lack of speed with which the IRB worked. In a few instances, the site visitors were concerned that so much had been done to promote efficiency (*e.g.*, through the use of subcommittees and primary reviewers) that too little was actually discussed by the IRB, which was in the position of being vulnerable to manipulation by primary reviewers.

Evaluating Specific Dimensions of IRB Performance. In addition to making an open-ended assessment of the IRB's strengths and weaknesses, site visitors were asked to rate IRBs on 16 specific dimensions. The separate ratings by 4 site visitors for each of 10 IRBs[12] (and a composite rating at 2 IRBs) are summarized in three tables.

The 16 dimensions on which site visitors were asked to rate IRBs are shown in the left column of Tables 3 and 4. Site visitors were asked to judge whether a genuine process of ethical review was taking place, whether the IRB was following the regulations and applying them reasonably, whether it was giving proper weight to the rights and welfare of subjects,

[12] Although the response categories were not used for the first three visits, it was generally possible to identify site visitor's comments as positive or negative. This was done for analytical purposes. The ambiguity of the responses of one or two site visitors on one or two questions was a reason the forms were changed to include rating categories.

whether it was placing unnecessary obstacles in the way of research, and so forth.

The second column in Table 3 shows the extent to which site visitors were able to rate IRBs in response to each of these questions. In response to many of the questions, all or virtually all the site visitors were able to rate each IRB. Site visitors had difficulty, however, judging whether the IRB was well accepted by researchers, since site visitors were dependent upon their conversations with preselected researchers for evidence. (At some IRBs, some of the researchers with whom the site visitors met had been selected because of their criticisms of the IRB; however, it seems likely that other institutions made no effort to bring their IRB's critics to the attention of the visitors.) It also proved difficult in some cases to judge how well the IRB was handling risk/benefit considerations, since this is a relatively intangible matter and is difficult to assess without attending a meeting. Difficulties were also experienced in assessing how well the IRB handled issues of confidentiality and privacy and their continuing review responsibilities. Site visitors had least success in assessing the adequacy of IRB policies and practices for investigation of complaints or problems that arise in the conduct of research, in part because most institutions reported that they had experienced no such problems.

Agreement among site visitors. Table 3 also shows the extent of agreement among site visitors in their assessments of the IRBs. For the most part, site visitors' ratings on specific items were either consistent (in general positive or negative terms) or one site visitor disagreed with the others who made ratings. However, on several items equal numbers of site visitors made positive and negative assessments of an aspect of an IRB. Post-site consultations among the visitors suggest that the basis for such differences can be identified and that differing views can be reconciled. Most of the differences were in the emphasis that visitors gave to particular observations, not from disagreements about what they had seen. However, these disagreements among site visitors suggest that assessments of these matters are best not put in the hands of a single reviewer; instead, there should be discussion and consultation among site visitors before final judgments are made.

The level of agreement among site visitors is shown on Table 3 (and is shown in another way on Table 5.) The relatively low agreement at several site visits seemed to be due to one of the two factors: (1) the visit was too short and visitors had too little information or (2) the IRB followed a rather unusual set of procedures that site visitors found difficult to assess. An important point is that experienced IRB members do not always come to the same conclusions about what they see; disagreement seems most likely to occur when the IRB's

Table 3:

Site Visitors' Ability to Rate IRBs on 16 Items

Evaluation Questions	% of 40 Visitors Able to Rate Item	Number of IRBs (out of 10)* on which Visitors Reached Various Levels of Agreement†			
		High	Medium	Low	N/A+
1. Is a genuine process of ethical review taking place?	100	6	1	3	0
2. How well is the IRB following the regulations & applying sound judgment thereto?	98	7	2	1	0
3. Does this IRB give proper weight to protecting subjects' rights and welfare?	100	4	4	2	0
4. Does this IRB place unnecessary or unreasonable obstacles to research?	95	6	3	1	0
5. Does this IRB have adequate support from the institution's administration?	100	7	2	1	0
6. Does this IRB appear to have good acceptance from investigators?	88	4	3	3	0
7. Does this IRB have clear and adequate authority?	98	7	3	0	0
8. How adequate is the range of issues with which this IRB is concerned?	93	5	3	2	0
9. How adequate is this IRB's composition, in light of amount and types of research reviewed?	100	4	4	2	0
10. How adequate are its procedures, in light of the amount & types of research reviewed?	100	5	2	3	0
11. How adequate is its record keeping?	100	5	3	2	0

Evaluation Questions	% of 40 Visitors Able to Rate Item	Number of IRBs (out of 10)* on which Visitors Reached Various Levels of Agreement†			
		High	Medium	Low	N/A+
12. How adequate is its handling of risk/benefit considerations in review?	85	6	3	1	0
13. How adequate is its handling of informed consent issues?	100	5	3	2	0
14. How adequate is its attention to issues of confidentiality and privacy?	70	7	1	1	1
15. How adequate are its policies and practices regarding continuing review?	90	6	2	2	0
16. How adequate are its policies and practices for complaint investigation or other problems that may arise in the conduct of research?	45	2	0	2	6

* Excludes 2 site visits at which group, but not individual, ratings were made.

† Site visitors checked one response category on each evaluation question. For the analysis of agreement among site visitors, their responses were coded as either favorable or unfavorable; noncommittal responses are not included. High agreement means that these responses were either all favorable or all unfavorable. Low agreement means that responses were equally divided between favorable and unfavorable ratings. Medium agreement means that 3 of 4 (or 2 of 3) site visitors were in agreement.

+ No measure of agreement is possible when fewer than 2 site visitors rated an item.

Table 4:

Variations Among IRBs on 16 Items Rated by Site Visitors (Based on 12 Site Visits)

Evaluation Questions	Mean Ratings on 5 Point Scale*		
	Highest Rated IRB	Lowest Rates IRB	All IRBs
1. Is a genuine process of ethical review taking place?	1.0	3.8	2.0
2. How well is the IRB following the regulations & applying sound judgment thereto?	1.0	4.0	2.3
3. Does this IRB give proper weight to protecting subjects' rights and welfare?	1.3	4.0	2.4
4. Does this IRB place unnecessary or unreasonable obstacles to research?	1.0	5.0	2.2
5. Does this IRB have adequate support from the institution's administration?	1.0	2.5	1.6
6. Does this IRB appear to have good acceptance from investigators?	1.6	5.0	2.4
7. Does this IRB have clear and adequate authority?	1.0	3.0	1.4
8. How adequate is the range of issues with which this IRB is concerned?	1.0	5.0	2.2
9. How adequate is this IRB's composition, in light of amount and types of research reviewed?	1.3	3.1	2.2
10. How adequate are its procedures, in light of the amount & types of research reviewed?	1.0	5.0	2.4
11. How adequate is its record keeping?	1.0	3.8	2.1
12. How adequate is its handling of risk/benefit considerations in review?	1.4	4.0	2.2
13. How adequate is its handling of informed consent issues?	1.0	4.0	2.2
14. How adequate is its attention to issues of confidentiality and privacy?	2.0	4.0	2.3
15. How adequate are its policies and practices regarding continuing review?	1.8	4.3	2.3

Evaluation Questions	Mean Ratings on 5 Point Scale*		
	Highest Rated IRB	Lowest Rates IRB	All IRBs
16. How adequate are its policies and practices for complaint investigation or other problems that may arise in the conduct of research?	1.0	5.0	2.6

* 1 = most positive; 5 = most negative.

procedures differ from those with which the site visitors are most familiar.

Variation among IRBs. An indication of the extent of variation among IRBs is provided in Table 4, which shows, item by item, the highest and lowest ratings of IRBs (based on the average of four site visitors' ratings at each IRB). On most items, there were large differences among IRBs. The two items on which even the best IRBs were seen as departing at least slightly from the optimal situation were: (1) acceptance of the IRB by investigators and (2) policies and practices for continuing review. This will not surprise anyone familiar with IRBs. The item that received the least negative response by site visitors was the adequacy of institutional support. No IRB was seen as seriously deficient in this regard. On all of the other dimensions, the least favorable assessments of an IRB ranged from neutral to negative. Although this presentation of the data is rather crude, it does suggest that site visitors perceive differences among IRBs on all these dimensions of IRB activity.

The final column of Table 4 shows the mean rating of each dimension at the 12 IRBs that were visited. It shows that on all 16 dimensions, the average IRB visited was rated positively by the site visitors. Thus, while site visitors perceived wide variations in the performance of IRBs on these various dimensions, on every dimension the majority of IRBs were seen as performing relatively well.

Table 5 provides another indication of the variations among IRBs and presents data separately for each of the 12 site visits. Column 2 shows the percentage of site visitors able to rate each IRB on each of the 16 items. Column 5, which shows the average rating of the four site visitors for all 16 items at each site visit, provides a summary measure of the extent of perceived variations among the 12 IRBs visited. On ratings based on a 5-point scale, with 1 being the best rating and 5 the poorest, the average scores for IRBs ranged from 1.5 to 3.3. (Since 3 is the midpoint on a 5 point scale, only 1 of the 12 IRBs was rated negatively when site visitor ratings across all items were pooled.) Again, this presentation of the data shows that

Table 5:

Ratings by Site Visitors of 12 IRBs

Site Visit Number	% of Visitors Able to Rate IRB on 16 Items Visit Number	Mean of Visitors' Ratings (Using 5-point Scale)†			Number of Items (out of 16) on which Visitors Reached Various Levels of Agreement°			
		IRB on 16 Items (n = 64)	Highest Rated Item	Lowest Rated Item	Rating on All Items	High	Medium	Low
1	98	1	2.1	1.7	12	4	0	0
2	85	1.2	3.5	2.4	4	4	7	1
3*	92	1	2	1.5	15	1	0	0
4*	93	1	3.5	2.3	5	7	3	1
5	92	1	2.5	1.8	11	3	1	1
6*	84	1	3.5	2.4	2	6	5	3
7	89	1.5	5	3.3	12	2	2	0
8*	92	1.2	3	2.1	7	3	6	0
9	93	1	2.5	1.8	13	2	1	0
10*	92	1	3.8	2.1	5	7	3	1
11	**	1**	3**	1.6**	**	**	**	**
12*	**	1**	5**	2.7**	**	**	**	**

* Site visits that included attendance at an IRB meeting.

** At two site visits, no individual ratings were made. Thus, these figures are not means of individual ratings, but are the agreed-upon ratings of the team.

† 1 = most positive; 5 = most negative.

° Site visitors checked one response category on each evaluation question. For the analysis of agreement among site visitors, their responses were coded as either favorable or unfavorable; noncommittal responses are not included. High agreement means that these responses were either all favorable or all unfavorable. Low agreement means that responses were equally divided between favorable and unfavorable ratings. Medium agreement means that 3 of 4 (or 2 of 3) site visitors were in agreement.

+ No measure of agreement is possible when fewer than 2 site visitors rated an item.

the site visitors' assessments of the IRBs were in general relatively favorable. Columns 3 and 4 show the high and low ranking on any item for each IRB.

The Value of Site Visits. Each site visitor was asked at the end of the site visit (or pair of site visits) for written responses to a series of questions about the usefulness of the site visits both as educational functions and for identifying problems that could be corrected by the institutions. Site visitors were also asked how these site visits could be improved. Some of these suggestions were incorporated into later site visits that were conducted for the Commission.

Site visits as an educational device. Only about half the site visitors thought the site visits as conducted were unequivocally useful as an educational device for the institutions. These conclusions were probably based on the amount of exchange of ideas that took place between site visitors and the persons with whom they met. It was not unusual for site visitors to be asked how their IRB handled some particular problem.

Most site visitors, however, indicated that such site visits have the *potential* for being educational for the institutions visited, and suggested that this will depend upon the tone of the visits, the attitude of the institution visited, the amount of information exchanged, and the quality of the feedback given to the institution.

Most visitors found the site visit educational for themselves.

Site visits for assessing IRB performance. Virtually all the site visitors indicated that they had felt able to make at least a reasonably firm assessment of the IRB visited. The factor most often mentioned as crucial in this regard was attendance at the IRB meeting. Comments ranged from its being "very useful" to the statement that "nothing will substitute" for it, although the instances in which most substantive discussion takes place in subcommittees raises the question of which meeting should be attended. As one indication of the importance of attending the meeting, it appeared that many of the questions raised by site visitors during the part of a visit that preceded the IRB meeting were aimed at trying to envision what the IRB's meetings must be like.[13]

In none of the visits at which a meeting was attended did the site visitors' review of an IRB's procedures, conversations with investigators and IRB members, and review of records fully prepare them for what they observed in the IRB meeting itself. Indeed, there were instances in which the site visitors' views of the IRB were substantially altered by the meeting; favorable initial impressions of procedures and the knowledge and concern of members were sometimes at odds with the quality of discussion in the meeting. The challenge for the visitors in such instances was to understand why the process did not work as well as it seemingly should have. In some instances the site visitors interpreted problems that appeared in the meeting as a function of the committee composition or its

[13] A possible alternative to attendance at the IRB meeting that was considered but not tried was the reconstruction of the review of particular proposals reviewed in the past. This could be done through the use of records, conversations with IRB members about issues that were discussed and decisions that were made, and conversations with the investigator. Some site visitors felt that this would be useful, while others did not, citing problems of artificiality, confidentiality, representativeness, and the limitations of recall.

leadership, while in other instances it appeared that some aspect of the IRB's procedures was causing problems. Thus the site visits that included attendance at an IRB meeting revealed the limitations of using an institution's written assurance of compliance with the regulations as an indicator of good implementation of the regulations.

Site visitors could usually reach general agreement about whether an IRB is giving proposals a review that is reasonably thorough, knowledgeably performed, and efficient. However, variations among site visitors occurred in their initial, individual assessments of many aspects of an IRB's functioning. To some extent, this appears to be a result of variations in the previous experiences and expectations of the site visitors themselves, most of whom had had previous exposure only to their own IRBs.

Administrative Matters. Most site visitors found a one-day site visit sufficient for a good general assessment of an IRB. (More time would be required if the site visitors were expected to make detailed comparisons of consent forms and protocols or if their conclusions had to be fully documented.) Several, however, felt that one and one-half to two days should be allocated, with the team receiving a general orientation and perhaps attending the IRB meeting on the first day, then meeting with IRB members and investigators and reviewing records on the second day. Most found the basic elements that were included in these site visits to be important and helpful—advance information about the IRB, orientation meetings with the chairperson and/or administrator, meetings with IRB members and investigators (either individually or in groups), and attendance at the IRB meeting. Some felt that being sent information in advance was very helpful; others felt that the necessary information could be quickly obtained on site. It was particularly useful to begin the site visit by having the chairperson describe how a proposal is processed from the time of its submission until disposition by the IRB. Where circumstances precluded an initial meeting with the chairman, the visit went less smoothly and had less focus.

Site visitors did not always believe that they had been able to have really open, frank discussions with IRB members and investigators. In some cases the team met with IRB members or investigators in groups; in other cases, they met individually. Occasionally, the chairman or other institutional officials were present during such meetings. Although holding meetings in groups increases the number of people with whom the site visit team can visit, individuals sometimes seemed to be inhibited by the group setting. This was particularly true of meetings with IRB members. On more than one occasion, site visitors were taken aside by individual IRB members and told that the group format precluded full candor. The presence of

the IRB chairman or other institutional officials during interviews seemed to have a similar effect. Group inhibition seemed to be less of a problem in meetings with investigators than in meetings with IRB members, perhaps because the subject matter was less sensitive (they were asked about their own experiences with the IRB and about how the IRB is generally viewed among their colleagues) and perhaps because ongoing relationships were less often at stake. Thus, one of the changes that took place between early and later site visits was the recognition that meetings with IRB members should be held individually, with no other institutional officials present, but that meetings with investigators could be scheduled in groups.

In general, the reviewers found the composition of the teams of which they were a part to be satisfactory. The need was stressed for a diverse group of experienced persons—administrators, IRB members and chairpersons, medical and nonmedical persons. It was suggested by a few site visitors that teams of only two or three members might be sufficient, at least at some institutions. The need to match the composition of the site visit team to the institution visited was also noted.

Although the site visits on this project were organized so that visitors to a given IRB could share the same basic experience, that is not necessarily the only reasonable way to do site visits. Site visitors seem to have similar reactions to what they encounter, particularly if they have opportunities for discussion during the site visit. If site visits are conducted in the future, particularly at large institutions, increased division of labor among site visitors would have the advantage of exposing the visiting team to a larger cross-section of relevant information in a shorter period of time. More open exchanges might also take place if IRB members were to meet with individual site visitors rather than with the team.

An element of these site visits that should not be replicated if site visits are to be done routinely was the procedure of asking site visitors to provide independent assessments of the IRB. This had been useful for the Commission's project; however, it appears that discussion among site visitors of their impressions is a useful way of uncovering idiosyncratic responses and correcting some misconceptions.

Some site visitors felt that it would be better not to leave the selection of individuals with whom the team met completely in the hands of the institution visited. Critical perspectives could be filtered out, if local administrators were so inclined. If site visits are to be performed for monitoring purposes, the site visit team could select in advance (perhaps from a listing of investigators and IRB members) the persons with whom they will meet.

Conclusions

The site visits conducted for the Commission suggest that there is a need for improvement in the institutional implementation of Federal rules for protection of human subjects. Site visitors had serious concerns about important aspects of 4 of the 12 IRBs visited, and had less serious reservations about 5 others. No serious violations of Federal rules were discovered; rather, deficiencies appeared to derive primarily from lack of clarity as to what is expected of IRBs in certain situations.

The focus of the site visits was not on regulatory compliance, nor did the site visitors attempt to second-guess IRBs' decisions, particularly about matters that are not amenable to clear determinations of right and wrong. Some of what the site visitors reviewed was factual in nature (*e.g.*, the composition of the IRB or the procedures that it followed).[14] However, some degree of judgment came into play on virtually all matters of concern to the site visitors—for example, whether the IRB was concerned with the appropriate issues, whether it kept good records, whether the consent forms seemed reasonably complete and understandable.

The site visitors were able to assess IRBs on a wide variety of dimensions. The IRB activities that most concerned site visitors were about matters that are not readily amenable to documentation. They arose when site visitors encountered a procedure or an orientation within an IRB that, based on their own experience, was undesirable either from the standpoint of protecting subjects or from the standpoint of avoiding unnecessary disruption of the research process. A particular strength of the site visit approach was that in many instances experienced outsiders could perceive problems or shortcomings in the IRB's performance as well as see connections between these problems and the IRB's composition, the way that it organized its activities, or the procedures that it followed in conducting its reviews.

The problems that, when encountered, the site visitors were most concerned about pertained to: (1) IRB procedures that reduce the probability of a full, effective review of proposals; (2) IRB members who lack a clear understanding of their role and responsibility; and (3) an occasional lack of institutional commitment to the spirit of the rules for protecting human subjects. Although there are undeniable differences among institutions in the work load that they place on the

[14] Some of the matters the site visitors were concerned with were factual in principle but the relevant data were not usually available (*e.g.*, the amount of elapsed time between the submission of a proposal and its approval, the number or percentage of proposals that were modified in certain ways as a result of IRB review, or investigators' opinions about the IRB).

review process, and institutions clearly need flexibility in how they implement the regulations, some procedural variations embody a degree of flexibility that does not seem desirable. At present, "IRB review" at one institution may mean a careful discussion by a committee, while at another institution it may mean individual reviews by as few as two "primary" reviewers, with the IRB's role confined largely to ratification of individual reviewers' decisions. Such differences must play a role in explaining some of the differences in IRB performance described at the beginning of this chapter.

In conclusion, it is clear that relatively brief site visits conducted by knowledgeable, experienced persons *can* identify problems in the operations of IRBs that are correctable by an institution once it has become aware that the problem exists.

Approaches to Evaluating IRBs

5

The Commission's site visit project was designed to try out a method for remedying several deficiencies in the Federal procedures for protecting human subjects: (1) Federal agencies generally know too little about how IRBs are implementing Federal regulations; (2) no satisfactory process currently exists for monitoring or improving IRBs; and (3) little clarity or consensus exists about how the performance of institutional review boards should be assessed. Although there was a sense that the assessment of an IRB was more than a matter of determining whether the IRB was meeting applicable Federal regulations, adequate standards for evaluating the performance of IRBs remained to be developed.

Important Areas of IRB Performance

To evaluate an IRB's performance, it is necessary to obtain information about various aspects of its functioning. The knowledge gained through the site visits conducted for the Commission has implications for understanding the functional importance of different elements of IRB performance—composition, procedures, and quality of deliberations and judgments. This last element is at once the most crucial and the most elusive of the items. IRB membership and procedures may be important determinants of the quality of its deliberations and judgments. By contrast, the quality of the consent forms or minutes may be an indicator of the presence of good deliberation and judgment. Various dimensions of IRB functioning may be used as indicators of IRB performance. The advantages and limitations of each are worthy of consideration. How can IRB performance be assessed, and are site visits necessary to do so?

IRB Procedures. One approach to assessing IRB performance (with or without site visits) might be the careful review of an IRB's procedures. This is important, but it is also of limited usefulness. Present regulations are not highly specific about procedures, and in the assurance process OPRR requires that institutions provide little information about the way their review process actually operates. Indeed, in the past there has been little explicit recognition by OPRR of the possibility that an IRB's procedures might affect the quality of its performance, although it has been known that there are great variations among IRBs in the procedures used to perform both initial and continuing review.[1]

Many procedural variations, which may have a substantial impact on the work of the IRB, were encountered in the site visits conducted for the President's Commission. For example, some of the IRBs gave proposals to primary reviewers, who are asked to review them on their own prior to the IRB meeting. The number of such reviewers ranged from one to a majority of the committee. Some primary reviewers were not IRB members. Some IRBs used subcommittees of various sizes and composition to perform an initial screening of protocols or to review technical aspects. At other IRBs, screening was performed either by the chairman or by an experienced administrative person. IRBs that use primary reviewers varied in whether reviewers were assigned in rotation or on the basis of expertise (*i.e.*, a perceived match between the reviewer's knowledge and the subject matter of the research). The IRBs varied in whether reviewers were allowed to negotiate with investigators, whether reviewers were expected to report in detail on the proposal as a way of initiating discussion in an IRB meeting, and whether reviewers were expected to make recommendations. The IRBs also varied in whether their informal norm was to accept the recommendations of primary reviewers with little or no discussion (which may happen most often when reviewers are assigned by perceived expertise) or to use reviewers' recommendations as starting points for discussions.

Some IRBs required investigators to submit proposed research in a particular format. Some investigators were limited (to as few as two pages) in the amount of information to be submitted to their IRB, while others were expected to provide the IRB with a copy (or multiple copies) of the entire protocol. In some IRBs all members received a copy of all

[1] Robert A. Cooke, Arnold S. Tannenbaum, and Bradford H. Gray, *A Survey of Institutional Review Boards and Research Involving Human Subjects*, in National Commission for the Protection of Human Subjects, REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, APPENDIX, U.S. Government Printing Office, Washington (1978) at 27-40.

materials submitted by the investigator, while in other IRBs a complete package was provided only to the primary reviewers or only to a reviewing subcommittee. Some IRBs encouraged specialization by members—for example, by expecting the lay members to review consent forms for readability—while others seemed not to encourage such specialization either implicitly or explicitly.

IRBs also differ in their norms and procedures for raising questions or requesting modifications. Some IRBs, for example, request further information from an investigator or modifications in proposals only if a majority of the IRB has voted to take these actions. Others transmit to investigators all serious questions or concerns raised in IRB meetings, without requiring a majority vote to do so. Still others allow or expect the chairman, a principal staff member, or primary reviewers to negotiate changes with investigators prior to the IRB's consideration of the proposal.

Some IRBs operate by consensus, although they may take formal votes for the record, while others operate on strict majority rule. Some IRBs expect investigators to attend meetings at which their proposals are discussed, while others view this as potentially inhibiting. Some attempt to assure the availability of investigators by telephone during IRB meetings, while others communicate with investigators almost exclusively in writing. Some boards conduct virtually all their work outside of the convened meetings (*e.g.*, through the use of individual primary reviewers, subcommittees, and the like), while the convened meeting is essentially the exclusive locus of effort for other IRBs. Some IRBs have checklists of varying degrees of elaborateness against which proposed research must be considered, while others provide no such detailed guidance for reviewers. Some IRBs have detailed guidelines for investigators, while others do not. Some IRBs have arrived at solutions to common problems that other IRBs might find useful. At present, few organized means exist for cross-fertilization.

But what does an IRB's procedures tell us about whether it does a good job? While a few procedures appear *a priori* to be inconsistent with an adequate review by the IRB (for example, providing copies of research proposals *only* to one or two primary reviewers), no empirical basis is available that systematically links procedural variations among IRBs to measure their performance. Furthermore, when one considers the diversity of institutions within which research is conducted and the great variations in the amount and types of research for which any particular IRB may be responsible, it seems unlikely that any one set of procedures could be shown to be better in all cases than others. Many different combinations of procedures may be workable. However, to determine how well

they work requires more than a review of the procedures themselves.

The Commission's site visits suggest that the procedures used by IRBs can usefully be considered in the context of a visit that recognizes the particular characteristics of the institution and the work load carried by the IRB, and that attempts to link procedures with the indicators of IRB performance that are accessible to site visitors. The ability to consider an IRB's procedures in the context of a particular institution and the particular composition of an IRB and its staff is one of the strengths of a site visit approach.

Composition of IRBs. Many of these observations about IRB procedures also apply to the composition of IRBs. The regulations include requirements regarding the size and composition of IRBs, but allow room for wide variation. The empirical literature shows no consistent relationships between IRB composition and IRB performance.[2] Furthermore, to know that an IRB's membership includes a psychiatrist, a lawyer, a minister, a surgeon, or several of such catagories reveals relatively little about the dynamics within the IRB, the quality of its discussions, or the seriousness with which it approaches its work. These important dimensions seem as likely to be influenced by the individual characteristics of the particular psychiatrist, lawyer, minister, or surgeon as by the fact that members of such professions are included on the committee. Yet it seems plausible that some variations in IRB composition may affect deliberations and decisions.

An advantage of a site visit, as compared with a review of members' qualifications, is the opportunity it provides to make direct observations about aspects of the IRB's performance that might be affected by its composition. For example, the extent, ease, or effectiveness with which a lawyer or minister participates in an IRB meeting tells much more about such a person's impact on the IRB than does the fact that a person with a given a set of credentials is a member. Viewing the manifestations of the implicit assumptions under which a committee operates tells more than does a review of members' qualifications. The concerns or sophistication of particular members can be assessed only in discussion with them or through observation of IRB meetings. Again, given the diversity among institutions in IRB procedures and in the volume and types of research with which their IRBs must deal, the practical effects of the composition of a particular IRB can be assessed only through a site visit.

Quality of Deliberations. In evaluating an IRB, the actual decisions it makes may be less important than its careful

[2] *Id.* at 60-63.

consideration of the issues presented by proposed research. The issues that merit discussion vary from protocol to protocol, depending on such factors as the nature and purpose of the research intervention, the characteristics of the subjects, and the adequacy of the provisions for informed consent. An IRB's discussions may or may not focus on important issues, may or may not reflect some sophistication about the issues, and may or may not reflect appropriate differences in points of view. The quality of such deliberations can be assessed with confidence only through a site visit.

IRB Decisions. If it were somehow possible (not to mention desirable) to state in advance all of the precise conditions that would have to be met in order for the rights and welfare of human subjects to be protected, it would be easy to tell if an IRB is performing well. Indeed, such rules could be implemented or checked automatically, perhaps by a computer. However, that is not the nature of the task presented to IRBs. While it has been possible to break down 'protection of human subjects' into some components (informed consent, risk/benefit, equity, privacy, etc.), and, in the case of informed consent, to make the concept more concrete by identifying the types of information that should be disclosed to prospective subjects, the inescapable fact remains that IRBs must make a series of *judgments*. Thus, the question of whether an IRB is protecting the rights and welfare of human subjects is in a sense a question of whether the IRB is making "good" or "reasonable" judgments.

To assess the quality of the outcome of an IRB's activities (*i.e.*, its judgments), it is necessary in turn to review the facts of particular research protocols. The degree of certainty with which the rightness or reasonableness of IRB decisions can be judged will vary according to the decision in question and the available facts. One can posit examples in which almost any person who was given the facts would reach similar conclusions. Any knowledgeable person would agree, for example, that there is a flaw in the consent procedure in a study involving administration of a toxic drug if subjects are not informed about the risks. However, most of the issues with which IRBs are concerned are less straightforward. The question is more likely to be how toxic the agent is, how important the study must be to justify exposure of human subjects to various levels of risk, how trivial or improbable a risk must be before it need not be disclosed to prospective subjects, and so forth. The ethical review of proposed research projects always involves a series of complex and interrelated judgments.

At times arguments are made that a given IRB decision was wrong or unreasonable. Such arguments will be of greater or lesser persuasiveness, depending on the facts of the

situation. Nevertheless, it is apparent that there are real difficulties in attempting to evaluate the adequacy of IRB implementation of rules for protection of human subjects by asking if the IRB made good decisions. Such evaluations depend to some degree on whether the observer agrees with the committee's judgment and, if not, the strength of the opposing argument. But who would be in a position to declare the winner in such an argument? Should the outcome be taken as an indicator of the adequacy of the implementation of the regulations? Such questions led the National Commission to caution against using site visits or audits as a means of questioning an IRB's substantive decisions.[3]

Nevertheless, persons who are knowledgeable about ethical issues and experienced in the review of proposed research may agree about whether the IRB is familiar with the regulations, whether its review addresses significant issues (about the rights and welfare of subjects) raised by the research in question, and, in light of these matters, whether a given decision is reasonable. For example, consent forms that have been approved by an IRB can be examined for obvious omissions or for unnecessarily complex language. Knowledgeable persons may also be able to agree about whether an unreasonable IRB decision is important or trivial.

Of more importance than the reasonableness of any given decision is the question of whether there is a pattern of such decisions, and, if so, what may explain such a pattern. A pattern may reflect lack of attention to certain values or types of concern (*e.g.*, the rights of human subjects or the requirements of good research design) or a misunderstanding of regulatory requirements. Such problems may, in turn, reflect on the competence of the IRB members or on the procedures that the IRB follows. A site visit provides a unique opportunity to observe the possible relationships between IRB decisions and IRB procedures and composition.

Purposes of Site Visits

The approach that is most suitable for site visits will depend on several factors such as cost, logistical feasibility, and purpose. Two important purposes for site visits have been identified: (1) to determine whether IRBs are complying with Federal regulations and (2) to enhance the sophistication and procedural soundness of IRBs. These are related—but distinct—goals.

The first purpose is to meet a legitimate need of Federal agencies that support or regulate research; the second is to

[3] National Commission for the Protection of Human Subjects, REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, U.S. Government Printing Office, Washington (1978) at 12.

stimulate improvements at the institutional level. To some extent, a review or monitoring process will necessarily be oriented toward both compliance and improvement. That is, a review process that is designed to assure compliance with the regulations must inevitably include some elements of education; the reverse is also true. Yet some differences in approach may be needed, depending upon whether the purpose is primarily to ensure compliance or to educate IRBs, or both.

A compliance-oriented monitoring process should be based on objective criteria, since an institution could hardly be deemed out of compliance without a showing that it has failed to meet clear and objective standards. The credibility of a compliance-oriented approach rests on unequivocal evidence. The effectiveness of an educational approach rests to a greater extent on the credibility of the reviewers and on the persuasiveness of their analysis of problems and suggestions for improvements. The approach explored here can examine both objective evidence and more general (or less concrete) questions about whether the IRB process is working well.

Comparison of the Commission and FDA Approaches to Site Visits

The peer-based site visit approach explored by the Commission was seen at the outset as contrasting with the inspection approach used by the FDA. The FDA approach, described in detail in Chapter Three, is based on visits to IRBs by FDA field investigators. FDA's approach also reflects the fact that it is a regulatory agency, although FDA officials emphasize that their inspection program is not designed to be punitive and is intended to provide useful suggestions to IRBs, not just to monitor for regulatory compliance. However, since the FDA does not routinely collect basic information prospectively about the IRBs that review studies under its jurisdiction, and since FDA does not maintain a list of approved IRBs (as does NIH), the FDA must confirm through inspection such information as that the IRB indeed exists, that its composition meets regulatory requirements, that it has a set of acceptable written procedures, and so forth. Thus there are reasons to expect some differences in the results of the peer site visits used in the Commission project and the FDA's approach.

After the completion of the Commission's site visits, the FDA provided the Commission with copies of some of its letters to institutions reporting the conclusions of the FDA inspections. This made it possible to compare the results of the FDA inspections and the Commission's site visits.

The first comparison was based on six letters, written from FDA headquarters to institutions, describing FDA's evaluations of their IRBs based upon the reports prepared by field investigators. These letters were selected by FDA to illustrate

Table 6:

Classification of 43 FDA Criticisms of Six IRBs (1981-1982)

Type of Criticism	Subject of Criticism			
	Formal Institutional Guidelines or Written Procedures	IRB's Actual Mode of Operation	Review of a Particular Project	Total
Failure to Meet Regulatory Requirement	14	9	9	32
Criticism and/or Advice	0	8	3	11
Total	14	17	12	43

how its inspections go beyond regulatory issues; thus, they are not necessarily representative of all such letters from FDA to institutions.

The six letters contained 43 items about which changes were either required or suggested. The Commission staff classified these items along two dimensions: (1) whether or not the comment concerned a failure to meet FDA regulatory requirements, and (2) whether the comment concerned (a) the institution's written guidelines or descriptions of procedures, (b) the IRB's actual mode of operation, or (c) the IRB's review of a particular project.

Table 6 shows the distribution of the 43 points that these letters called to the attention of these six IRBs. Three-quarters of the points raised (32 comments) pertained to failures to meet regulatory requirements. Most frequently, these consisted of shortcomings in the institution's written procedures and guidelines. Problems included such matters as the failure to have the qualifications of IRB members on file and the lack (or inadequacy) of written guidelines and procedures about such matters as quorum requirements, procedures for handling emergency uses of investigational drugs, elements of informed consent, and the basis for determining schedules of continuing review.

Nine points in the FDA letters concerned regulatory deficiencies in the IRB's actual mode of operation, such as the failure to review consent forms for accuracy and conformity with the regulations, the reliance on continuing review for all projects at the same fixed interval, inadequate documentation of an IRB's acceptance of review by another IRB in a

cooperative study, and the lack of an adequate system for ensuring that changes required by the IRB were actually made by investigators.

The third set of regulatory lapses pertained to the review of particular projects. Problems identified included: not conducting a continuing review until 17 months after the initial approval (the regulations require at least an annual review), having no record of continuing review of a project, inadequate documentation of IRB action regarding a particular proposal, failure to record the IRB's numerical vote, consent forms that did not include certain required elements (such as disclosure of alternatives and the name of a person to contact in the event of problems), consent forms that differed from the forms approved by the IRB, and lack of documentation that conditions imposed by the IRB had actually been met by investigators.

About one-fourth of the points raised in the FDA letters were criticisms or suggestions that were not tied to particular regulatory requirements. These points, most of which pertained to IRB procedures, varied in importance. Examples include suggestions to simplify the consent forms and put risks into lay language; to consider replacing members who rarely attend meetings; to have at least one member review the entire protocol, if summaries of protocols were used for IRB review; to have the entire IRB, not just the chairperson, review major changes in protocols made at the direction of the IRB; to distribute protocols (or summaries) and consent forms to all IRB members prior to meetings; to include in consent forms the name of someone other than the investigator (such as the IRB chairperson) who subjects could contact in the event of an injury or violation of their rights; and to meet more than once or twice a year.

Some of these concerns and suggestions are similar to those arising from the peer site visits performed for the Commission, as was described in Chapter Four. For example, the practice of limiting distribution of the research protocols to only some members of the IRB was criticized by both the FDA investigators and the Commission site visitors; so were uninformative minutes.

However, the overall tone of the feedback provided to institutions after the FDA inspections is quite different from that following the Commission's site visits. The FDA inspections and resulting comments focus more on regulatory matters and written guidelines than did the Commission's site visits. In addition, the letters provided by the FDA show little attention to many topics that were of concern to the site visitors in the Commission project. For example, many of the Commission's site visitors' comments concerned such matters as the composition of the IRB, the leadership and knowledge of the IRB chairperson, the degree of institutional support for the IRB,

delegation of the review process to primary reviewers or subcommittees, degree of emphasis on and quality of paperwork, the sense of purpose or commitment within the IRB, the quality of IRBs' discussions and decisions, the orientation or approach of the IRB, and IRB efficiency. With one or two exceptions, these matters were not raised in the FDA letters to institutions.

A second comparison of the FDA and site visitor approaches was based on visits to the same institutions. Following completion of the Commission's site visits, the staff requested copies of recent FDA inspection letters for a number of institutions. These letters showed that three of the institutions that had been visited in the Commission's project had also undergone an FDA inspection within four months of the site visits. Comparisons were then made of the results of the two visits at these three institutions.

Table 7:

Comparison of FDA and Site Visit Evaluations of Three IRBs

Institution A	
FDA Inspection (8/81)	Site Visit (10/81)
Our review of the findings revealed that the committee was operating in compliance with current regulations at the time of this inspection.	Major Strengths: Conscientious, respected membership Well-established routines; efficient operation Wide range of concerns; thorough Good communication with investigators Devoted chairman Good administrative support Major Weaknesses: Narrow view of consent; exclusive focus on forms. Much of IRB responsibility delegated to subcommittee that does not meet IRB membership or record-keeping requirements; excessive power and lack of accountability of subcommittee. Committee receives only a summary of protocols; many issues are not discussed in meetings of the IRB.

Institution B	
FDA Inspection (8/81)	Site Visit (including IRB meeting) (10/81)
Noted that "committee minutes should record the numerical vote on each committee action as required by" the regulations. (The institution had been recording some votes as "unanimous.") Noted that the handbook that had been prepared by the IRB was not up-to-date on consent elements required by the regulations (specifically, the notice to subjects that records are open to inspection by FDA was not present), although noted this element was included on a worksheet used by the IRB in reviewing the adequacy of consent forms. Noted that the IRB had made suggestions for improvement of all three consent forms reviewed by the inspector but that the IRB records did not contain subsequent copies of consent forms "which document that the appropriate changes were made." In reply, the institution explained that in one of these instances the IRB had never approved the project and that it had not been carried out, and that in the other two instances noted by the inspector the IRB's comments were suggestions for improving a consent form that the IRB had in fact approved. Since the IRB had not required that these consent forms be modified, their procedures did not require that modified consent forms be filed with the IRB. The FDA responded that this response was "quite satisfactory."	Major strengths: Very effective, well-organized IRB. Highly participatory. Shows good range of concerns. Problem-solving orientation. Knowledgeable, conscientious, respected chairman. Stable, diverse membership. Open communication with investigators. Members had a clear idea of what the function of an IRB should be, exercised their responsibilities knowledgeably, effectively, and did an excellent job in protecting human subjects. "Laymen" as well as experts were evaluating technical material and seemed fully able to do so. Committee especially helpful in matters of informed consent and risk/benefit ratio. Major Weaknesses: None Criticisms: One site visitor thought the IRB should add a statistician and have more staff support for the chairman.

Institution C	
FDA Inspection (1/82)	Site Visit (1/82)
Our review of the findings indicates that our committee was in compliance with Federal regulations at the time of this inspection.	Major Strengths: Capable membership and chairman; efficiency Major Weaknesses: (excerpted from team's letter to institution): Although site visitors felt that your institution is fulfilling the applicable regulatory requirements, there was concern that the IRB has lost its purpose to some extent and that subjects and investigators may be getting shortchanged. The procedures that have been adopted seem likely to greatly limit discussion by the IRB; this is confirmed by the very small amount of time per proposal spent on the review process at your institution. It was the group's impression that your IRB is primarily a creature of the regulations, not of conviction; that there may be a conflict of interest in the subservience of the IRB to the organized faculty; that the IRB is not very diverse in its composition; and that outside members may either be coopted or frozen out. The major concern raised by the group was with the primary reviewer system that is used in which other members of the IRB do not get a copy of the proposal. Essentially it appears that your IRB is using what amounts to an 'expedited review' for all proposals, and that the adequacy of the review of any particular protocol is almost completely a function of the adequacy of the review by the primary reviewer. Since other members of the IRB do not see the protocols there is almost no check on the adequacy of the review by the primary reviewer, and there is almost no chance that any issues other than those raised by the primary reviewer will be discussed by the IRB. Thus it is not very surprising that your IRB processes a very large number of protocols in a very short amount of time. Our group felt that the procedures that your IRB follows serve primarily the goal of speed and efficiency, and probably don't lead to a good, careful review of each protocol by the IRB.

Institution C	
FDA Inspection (1/82)	Site Visit (1/82)
	On any given proposal, only two committee members see it and only four committee members see the consent form. It is difficult to see how a good quality discussion can be held under such circumstances. We noted also that the records indicate that virtually all committee decisions are made unanimously. It appeared to us that the committee essentially relies on the primary reviewers and follows whatever recommendations that they make. This is not the true IRB process as it is understood by any members of our team. The fact that the IRB will not waive written consent requirements has probably discouraged research in which written consent is not a feasible requirement. Here, the IRB seems not interested in availing itself of the options available under the regulations. The records we reviewed were rather cursory. The minutes contain no hint of any discussion or of the major issues that were of concern in the IRB's review. One cannot tell from the minutes what happened at the meeting, other than which proposals were approved and so forth.

The two approaches produced dissimilar results. Two of the IRBs were found by FDA to be in compliance with the regulations, and no suggestions for improvement were offered. The Commission's site visitors noted only minor *regulatory* violations at these two IRBs (*e.g.*, the minutes of one showed that it had met once without a quorum present); however, at both institutions site visitors had some serious concerns. At the first institution, although the interests of subjects seemed to be reasonably well protected, the site visitors had reservations about IRB procedures that delegated much of the substance of the review process to another committee that met few of the requirements of an IRB (*e.g.*, it did not meet the membership requirements nor did it keep minutes). The use of this second committee was described, with no reservations, by the FDA investigator in his field report. At the second institution found satisfactory by FDA (Institution "C" in Table 7), the site visitors had major reservations about the institution's commitment to the purpose of the IRB, about the small amount of time devoted to actual IRB review of proposals, about a lack of diversity within the IRB and limited participation by outside members, and about the use of a primary reviewer system that effectively delegated the whole IRB function to primary reviewers.

The third IRB was given notice of several problems in the FDA letter, although the institution's explanations were later accepted. This IRB was evaluated very favorably by the site visitors, who attended an IRB meeting and had no serious reservations or criticisms.

The differences in the results of the two types of evaluation appear to reflect differences in approaches used. The assessments by the Commission's site visitors were more qualitative and oriented more toward the goals and purposes of IRB review than toward technical conformity with regulatory requirements. The FDA assessment of these IRBs appeared to depend heavily on regulatory compliance.

Since 75% or more of the IRBs that review FDA-regulated drug research do not review Federally sponsored research with human subjects[4] and hence have had no occasion to go through the advance "assurance" process that would bring them into formal compliance with the HHS regulations, FDA's emphasis on regulations may be appropriate. It may also be true that site visits of the type tried out by the Commission would be improved if the participants gave more attention to compliance with the formal requirements of the Federal regulations.

[4] Background information on FDA's IRB inspections prepared for the Commission by the Office of Associate Commissioner for Health Affairs, Food and Drug Administration, Washington, Oct. 1982.

Possible Auspices for a Site Visit Program

Although the Commission had some initial ideas about the elements that should be a part of the site visit approach to be explored—*e.g.*, site visitors should be experienced members or staff of IRBs—it began with no preconceptions about how a program of site visits might be implemented.

As the need for, and utility of, an IRB site visit program became apparent, the Commission considered the possible auspices under which it might be undertaken. An IRB site visit program could be patterned after (or draw elements from) several existing models. These models also provide a basis for estimating the costs that might be involved. One existing model is a governmental, regulation-based inspection program, such as is now conducted by the FDA. The FDA program was described in some detail in Chapter Three. Another major existing model is private, voluntary accreditation. A third model would be site visits under the auspices of Federal agencies.

The Accreditation Model. One option for establishing a program of quality review and education for IRBs is in the private sector. Many applicable elements for such a program can be found in the approaches used by accreditation bodies established to encourage and recognize high standards of quality in certain institutions. To better understand how accreditation programs work and the extent to which the accreditation model might be suitable in the IRB context, the Commission obtained information about two existing accreditation programs that deal with related issues—the programs of the Joint Commission on Accreditation of Hospitals and of the American Association for the Accreditation of Animal Laboratory Care.

The Joint Commission on Accreditation of Hospitals. JCAH is a private, voluntary organization that accredits not only hospitals but also a variety of other types of health care facilities, including long-term care facilities, psychiatric institutions, and ambulatory care facilities. More than 7400 facilities and programs participate in the JCAH program, including 75% of the acute care general hospitals in the U.S.

The stated mission of the JCAH is "to improve the quality of care and services provided in organized health care settings through a voluntary accreditation process."[5] JCAH develops standards of quality, organizes education and consulting programs, and conducts on-site surveys of facilities on which its decisions to award accreditation are based. JCAH accreditation has come to serve as an indicator of qualify health care,

[5] Joint Commission on the Accreditation of Hospitals, ACCREDITATION MANUAL FOR HOSPITALS, Chicago (1983) at v.

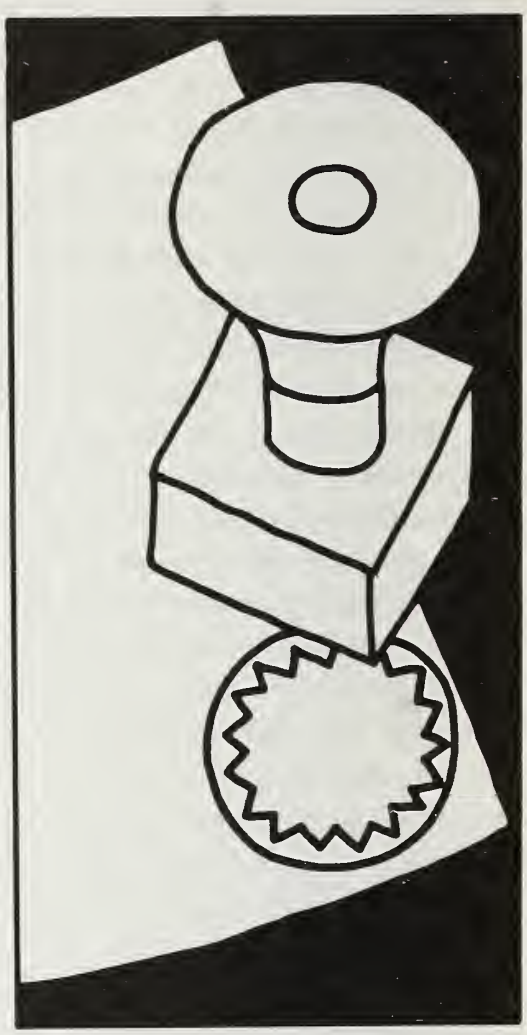
to qualify institutions for reimbursement for services from several insurance companies, to demonstrate compliance with certain Federal conditions of participation in the Medicare and Medicaid programs, to meet some budget and funding requirements, and to meet certain qualifications for some postgraduate medical education programs.

The member organizations of the JCAH are the American College of Surgeons, the American College of Physicians, the American Hospital Association, the American Medical Association, and the American Dental Association. The JCAH is governed by a 22-member board composed of individuals appointed by these organizations plus one public member. Separate committees are responsible for the ongoing development and revision of standards and survey procedures and for the actual decisions of whether to grant or withhold accreditation of a particular institution.

The JCAH was established in 1951, but its antecedents include the 1918 Hospital Standardization Program of the American College of Surgeons. The original JCAH standards of quality were based on this program, but these have undergone a series of revisions in what is described as an ongoing process. JCAH standards are intended to have certain characteristics: to relate to the quality of care or services provided, to "encourage excellence within available resources," to be achievable, and to be amenable to assessment (*i.e.*, compliance with them is measurable). The standards, which are published,[6] consist of a series of general principles, specific standards stating how the principles are to be applied, and detailed interpretations of the standards. The standards, which for hospitals address such topics as anesthesia services, building and grounds safety, the hospital's governing body, nursing services, and quality assurance, generally state an objective to be met but not the precise way that this is to be done.

Institutions seeking accreditation are expected to provide evidence of the extent of compliance with each standard. To be accredited, an institution must demonstrate "substantial compliance" with the standards. To this end, several means may be used, the most important of which is a mandatory, on-site visit by a JCAH survey team. To be eligible for an accreditation survey, an institution must meet certain eligibility criteria. For hospitals, these criteria include specific services that must be provided, organizational requirements (*e.g.*, it must have a governing body, an organized medical staff, and nursing service), certain functions for which provisions must be made (*e.g.*, infection control, medical records, a professional library, quality assurance), and so forth. Since separate standards and

[6] *Id.*



accreditation are offered by JCAH for acute-care general hospitals, long-term care facilities, psychiatric facilities and programs, and ambulatory health care organizations, a large and complex institution may be covered by several accreditation programs.

The composition of a JCAH survey team (usually three persons) depends on the type of institution being reviewed. For example, the team for a hospital survey would include a physician, registered nurse, and a hospital administrator (and sometimes a medical technologist), while the team to survey a long-term care facility would include an administrator, registered nurse, and/or social worker. The surveyors for hospitals are either full-time or part-time JCAH employees who meet specified requirements concerning professional experience (*i.e.*, the physicians should have five years experience as a hospital chief of staff, the nurses should have five years experience as a head of nursing in a hospital, and the administrators should have five years experience as a chief executive officer in a hospital). Some of the surveyors for other types of institutions are consultants to JCAH, rather than employees. JCAH has a regular training program for surveyors.

On the survey visits, which for hospitals typically last two or three days but which vary depending on the size and complexity of the institution, the team gathers the information needed to evaluate the facility according to the JCAH standards. Procedural guidelines developed by the JCAH indicate who should be interviewed, what documents should be reviewed, and which facilities should be toured by each member of the site visit team. Provisions have also been made for public notice in advance of the survey so that members of the public or the hospital staff can arrange to meet with members of the survey team. At the end of the survey, a "summation conference" is held, during which the surveyors present their findings for discussion and clarification, and representatives of the facility have an opportunity for comment.

The actual decision to award or deny accreditation is made by the Accreditation Committee of the Board of Commissioners. JCAH staff members evaluate first the results of the survey, the survey team's recommendations, and such factors as the institution's degree of compliance with past recommendations, as well as any firm plans it has to correct deficiencies. The staff then recommends to the Accreditation Committee that the facility either be accredited or be denied accreditation. If the recommendation is to deny accreditation, the institution is given an opportunity to provide additional information for the Accreditation Committee's consideration. A series of procedural safeguards and appeals mechanisms are available in such cases.

For institutions considering seeking accreditation for the first time, JCAH has developed an approach designed to maximize the educational value of the survey and to reduce the risk to which an institution may be exposed when voluntarily seeking accreditation (*i.e.*, the risk that the institution will be denied accreditation and be embarrassed). If the initial site visit to such an institution identifies so many shortcomings that accreditation cannot be granted, the visit is treated by JCAH as a consultation/education visit (*i.e.*, no official decision to deny accreditation is made or transmitted), and the institution receives extensive guidance on remedial steps needed for future accreditation.

JCAH accreditation is for three years, although accredited institutions must conduct a self-survey and submit a report to JCAH 18 months after the JCAH survey. An accredited institution may be surveyed at any time at the discretion of the JCAH. An institution that is not granted accreditation or that has had it withdrawn may apply for a resurvey, but this ordinarily cannot take place until six months after the final nonaccreditation decision.

JCAH treats all information obtained in the accreditation survey process as confidential. Unless otherwise required by law or requested by the facility, the results and recommendations of the survey are given only to the surveyed facility. (Provisions do exist for notification of state and local authorities if a serious condition is found that jeopardizes the public safety or the safety of a patient.) JCAH publishes aggregate data obtained through its surveys and will release certain information on request, including whether JCAH has received an application for survey from a particular facility, a list of facilities scheduled for survey, the survey date for a particular facility, and information about whether or not a facility is accredited. Under some circumstances (*e.g.*, where JCAH accreditation is being used to qualify an institution for some purpose), JCAH routinely responds to a standing request for information about whether or not an institution is maintaining

accreditation. For example, if JCAH accreditation is needed for a hospital's participation in the Medicare program, JCAH notifies the Health Care Financing Administration if the hospital loses accreditation.

The costs of the survey and accreditation process are borne by the institutions that seek accreditation. There is an application fee of $250. More importantly, institutions pay survey fees on a surveyor/day basis. In 1982, institutions paid the following fees for each day that each surveyor spent at the institution:

Hospital facilities	$1000
Long-term care facilities	$ 625
Psychiatric facilities	
Hospital-based	$1000
Non-hospital-based	$ 825
Ambulatory Health Care	$ 700

At an average hospital, a three-person team will devote two days to a survey. Thus, the hospital's cost for the JCAH survey would be $6000, although since accreditation is for a three year period, this cost is incurred only every three years. If follow-up visits are needed in the interim, additional charges are made.

Although a JCAH survey reviews the entire range of institutional functions, including functions that are more elaborate and complex than are the activities of an IRB, many elements of the JCAH's survey process are similar to elements that would be required in a program incorporating the type of site visit approach that was found by the Commission to be useful and worthwhile for IRBs. These include: the selection and training of surveyors or site visitors; the development and testing of standards; workshops and seminars to transmit information about the standards; the actual conduct of site visit surveys that include interviews, observations, and review of documentation; and the review of survey reports to determine whether institutional performance is satisfactory.

The American Association for Accreditation of Laboratory Animal Care. AAALAC is a voluntary accreditation body whose purpose is to encourage "optimal care for laboratory animals by providing a mechanism for peer evaluation of animal care programs by the scientific community."[7] It is concerned with the humane treatment of laboratory animals (*i.e.*, animals used in scientific research), the protection of personnel from hazards arising from the use of animals in research, and the control of "variables that could affect animal research adversely." Founded in 1965, AAALAC accredits facilities at more than 420 institutions including colleges and

[7] American Association for Accreditation of Laboratory Animal Care, informational brochure, Joliet, Ill. (n.d.).

universities, medical and dental schools, hospitals, Veterans Administration Medical Centers, pharmaceutical manufacturers, and research laboratories (government, commercial, and nonprofit).

AAALAC has a membership of 24 professional organizations in education, medicine, and research such as the American Association for the Advancement of Science, American Medical Association, American Hospital Association, American Veterinary Medical Association, Association of American Medical Colleges, National Association of State Universities and Land Grant Colleges, Federation of American Societies for Experimental Biology, and Pharmaceutical Manufacturers' Association.

AAALAC is governed by a Board of Trustees composed of a representative from each member organization. Accreditation decisions are based on information developed and reviewed by a 16-member Council on Accreditation appointed by the Board of Trustees that is responsible for conducting site visits to animal care facilities, evaluating site visit reports, and making recommendations to the Board regarding accreditation. The standard by which institutions are evaluated is the NIH *Guide for the Care and Use of Laboratory Animals*, which contains general recommendations about such matters as housing, sanitation, husbandry, and veterinary care of laboratory animals, the qualifications and protection of personnel, and the characteristics of the physical plant.[8] NIH recognizes AAALAC accreditation as demonstrating institutional compliance with its policies on the care and use of laboratory animals.

Institutions seeking acceditation must meet certain eligiblity requirements and complete an application describing the facilities, types and numbers of animals, and personnel involved. The decision to accredit is based on the factual findings of a site visit conducted by a two-person team of "experienced leaders in laboratory animal care"—ordinarily one member of the Council on Accreditation and one consultant drawn from a group of approximately 120 scientists approved by the Council.

The site visitors inspect the facility and evaluate all aspects of the animal care program. Site visits include a combination of interviews, review of policies and records, and observations of facilities, and can last from one to several days, depending on the number and size of facilities at the institution. The intent is to cover every point in the *Guide*. After the visit, a detailed written report is prepared and

[8] National Research Council, Guide for the Care and Use of Laboratory Animals, U.S. Government Printing Office, Washington (1978).

submitted to the Council on Accreditation. This report forms the basis of the Council's accreditation decision, which is subsequently confirmed by the Board of Trustees. Institutions either receive full or continued accreditation, or provisional or probationary accreditation (when serious but correctable deficiencies are found that require a subsequent determination or site visit), or have accreditation withheld or revoked. The institution is then sent a letter summarizing the conclusions of the Council.

Fully accredited institutions receive a site visit every three years. In 1981, approximately 160 visits were conducted, of which 130 were at accredited institutions and 30 at institutions applying for accreditation.[9] Accredited institutions must also submit a report every year describing changes in such matters as personnel, equipment, facilities, sanitation practices, disease control practices, euthanasia techniques, surgical techniques, and the animal population (by species).

AAALAC's confidentiality policy is more stringent than that of the JCAH. The only information that AAALAC will release is a list of institutions that are accredited.

Applicants pay an application fee of $525-$825 or more, depending on facility size, characteristics of the animal population, and the amount of time needed to conduct the visit. In the years that they are not visited, accredited institutions pay an annual fee equivalent to the application fee. AAALAC's 1981 budget was approximately $265,000.[10]

Applicability of the Accreditation Model to IRBs. The use of private accreditation bodies for IRB site visits has several attractive features. Clearly, accreditation organizations have considerable experience with activities that have much in common with site visits to IRBs. The problem of developing criteria and standards, conducting visits, developing due process protections and so forth are familiar ones to such organizations. Conducting site visits through organizations in the private sector could lessen the regulatory flavor of the visits, although this might depend upon whether accreditation were to become a condition of eligibility for research funds. The more that rests on the outcome of the visits, the less likely they are to be relaxed and collegial. It is also possible that some potential site visitors would be more willing to participate in a voluntary program than in a governmental program.

On the other hand, although several extant organizations have expertise in site visiting and accreditation, no accreditation body in the private sector has specific expertise in the work of IRBs and no organization having expertise with IRBs

[9] Information provided by personal communication with Lee A. Heilman, Executive Director, AAALAC, Oct. and Nov. 1982.
[10] *Id.*

has experience with site visits and accreditation-like activities. Furthermore, no existing private organization has jurisdiction over, or a constituency of, the organizations that have assurances of compliance with the HHS regulations for research involving human subjects.

Finally, if a private sector program of site visits were contemplated, questions would have to be resolved about many fundamental issues such as auspices for the program, liaison with OPRR, funding for the program, and the way regulatory violations would be treated by site visitors (*i.e.*, whether noncompliance would be reported to OPRR or FDA, and, if not, whether the program would meet their needs for accountability). Also, site visitors from a private organization might be reluctant or unable to give definitive advice to an IRB on whether its policies and practices comply with regulatory requirements; if they gave advice that OPRR or FDA did not accept, institutions that followed the advice might be in an awkward position.

Site Visits via Regulatory Agencies. The IRB-related activities of the Food and Drug Administration and the NIH Office for Protection from Research Risks, two major governmental agencies with regulatory authority over IRBs, were described in some detail in Chapter Three. A second approach for establishing a regular site visit program would be to incorporate it into existing programs. This could be done separately by different agencies, or it could be done through a joint program. For example, some IRBs that now review FDA-regulated research are on the OPRR list of approved IRBs, and FDA sends OPRR copies of all correspondence with those institutions about previous inspections. Those IRBs could be the focus of a joint OPRR/FDA evaluation program. Alternatively, if FDA were to adopt the assurance system now used by OPRR, a coordinated site visit approach could be used with all IRBs within the jurisdiction of HHS.

Whether or not a joint FDA/OPRR approach proves feasible, there are advantages in locating a site visit program within existing regulatory programs. It would build on existing expertise regarding IRBs and the regulations governing research with human subjects. It would ensure that the site visits would be relevant to the responsibilities of the agencies that administer the regulations, and it would facilitate the use of the site visits to provide authoritative advice regarding compliance with the regulations.

A major advantage of establishing a site visit program in OPRR is that, as a result of the assurance process, it already has linkages to all of the major IRBs (and to many small ones as well). Furthermore, unlike any accrediting body, OPRR's present jurisdiction perfectly encompasses the institutions that have general assurances. Location of a site visit program

elsewhere would necessitate duplication of many records and would create a need for establishing new lines of communication. OPRR has extensive records on existing IRBs in the form of assurances, IRB rosters, and files on past problems, and it is establishing a mechanism to collect and analyze reports on problems identified by study sections regarding IRB-approved research. Collectively, information of this sort would provide a basis for establishing the frequency with which an institution should be visited or for selecting institutions for site visits. Location in OPRR or FDA would also provide leverage for change in those IRBs that need improvement.

In addition, building on the FDA/OPRR base would minimize start-up costs. If resources now devoted by FDA to inspections at institutions having assurances with OPRR could be shifted to the site visit program, this would reduce the need for new funds.

Further, although there are exceptions, OPRR also seems to have generally good relations with institutions and seems to be oriented toward education and cooperation in improving the functioning of IRBs. OPRR has informed the Commission over the past three years of its interest in developing a program of site visits and has expressed an interest in applying the knowledge gained in the Commission's project.[11]

Among the possible problems raised by establishing a regular site visit program within an existing governmental agency is the possibility that a heavy regulatory flavor would thereby be imparted. Despite the generally good relations between OPRR and research institutions and FDA's efforts to improve its inspection program, the question remains whether a site visit program within a government agency could maintain an educational/collegial focus. It is also unclear whether such a governmental location for a site visit program would affect the willingness of experienced IRB personnel to serve as site visitors.

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[11] The Commission believes that institutions should be encouraged to go through the process of obtaining a "multiple project" or "general" assurance of compliance. However, it is likely that some research that is subject to Federal regulations will continue to be conducted at institutions where only a single project exists. For such institutions an assurance process along the lines of the "single project" or "special" assurances negotiated by OPRR may continue to be efficient and appropriate. It is probably not cost/effective to attempt to include such institutions in a site visit program of the sort that the Commission recommends. For such IRBs, the FDA inspection program will continue to play a useful role by keeping sponsors and investigators on notice that non-compliance may be detected.

Cost of a Site Visit Program

The precise cost of a site visit program could only be determined if detailed assumptions were made about such matters as the feasibility of attaching it to an ongoing program (thus sharing some fixed costs), the inclusion of only the IRBs on the OPRR-approved list, the number of visitors per institution, the length of a typical site visit, the frequency with which institutions would be visited, the extent of other educational or research activities that would be connected with the program, and so forth. However, an estimate of the range of costs within which a program could be established and budgeted can be drawn from an examination of the costs associated with the three programs described earlier in this Report.

The American Association for the Accreditation of Laboratory Animal Care conducts approximately 160 site visits per year, using two-person teams for visits that are usually one day in duration. The total budget in 1982 was $265,000.[12] Thus, the cost of an AAALAC accreditation review is approximately $1560 per visit.

The fees charged by the Joint Commission on the Accreditation of Hospitals to cover the costs of its programs are expressed on the basis of site visitor days (*i.e.*, an amount per site visitor per day). JCAH teams are usually composed of three persons, and a JCAH inspection covers a far wider range of topics than would be covered in an IRB site visit program. Although the JCAH fee for hospital accreditation visits is $1000 per site visitor/day, its visits to less complex institutions are billed for as little as $625 per visitor day (at long-term care and ambulatory care facilities).[13] Using the latter figures, a hypothetical one-day, two-person visit at JCAH rates would cost $1250.

FDA's costs for IRB inspections include both the costs associated with field investigators (who each spend on average approximately 3.5 days per inspection, including preparation time, one day on site, and time to write a report) and headquarters personnel (who spend an average of 2.5 days per inspection, reviewing the materials submitted by the field investigators and preparing a report to the institution). FDA's estimate of the cost per visit is $1134.[14]

At the present time, the OPRR list of institutions that have provided satisfactory multiple-project assurances of compliance with the HHS regulations includes approximately 450 institutions, having a total of approximately 600 IRBs.[15] If each

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[12] *Supra* note 9.

[13] Figures provided by JCAH Executive Office.

[14] Letter from Dr. Stuart L. Nightingale, Associate Commissioner for Health Affairs, FDA, to Bradford H. Gray (Sept. 8, 1982).

[15] This figure, which was provided by OPRR, pertains only to

IRB were visited every three years, approximately 200 visits per year would be required. Using the range of figures described above, a program that had two people visiting 200 IRBs for one day per year would cost $225,000-$330,000 annually.[16]

The FDA already spends between $75,000 and $100,000 per year on inspection visits at institutions on the OPRR list.[17] If the resources spent for inspections at these institutions were shifted to a site visit program, an additional $125,000-$255,000 would be needed.

A comparative perspective on costs is useful. The prospective costs of an IRB site visit program, using the assumptions described above, are comparable to the amount now spent on the animal lab accreditation activities of AAALAC ($265,000). Another point of comparison is the existing budget for OPRR, which was estimated at $795,000 for FY 1982.[18] The funds required for the site visit program would thus represent a 15%-32% increase of the OPRR budget.

Perhaps a more relevant perspective on costs comes from considering a site visit program in relation to other NIH activities. The total NIH budget in FY 1982 was approximately $3.6 billion; the total amount spent by NIH in grants and

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"multiple project" (formerly called "general") assurances of compliance, for IRBs established on a continuing basis (and so recognized by OPRR) to provide institutional review for an indefinate period of time (usually, for many years). Essentially, these IRBs are accepted by OPRR as being in compliance with the HHS regulations, and approval by the IRB meets HHS's institutional review requirements. If an institution not having a multiple project assurance wishes to submit to HHS a proposal for research involving human subjects, it must demonstrate compliance with the human subjects regulations by negotiating with OPRR a "single project" (formerly called "special") assurance. OPRR reports that it has approximately 2000 single project assurances active at any one time (average duration, three to five years). As the name implies, OPRR accepts such assurances of compliance only for purposes of IRB review of a particular project; the assurance process would have to be repeated if the institution were to submit another proposal. Understandably, for institutions that seek Federal research support with any frequency, both OPRR and the institutions find it much more efficient to negotiate a multiple project assurance. It seems sensible to confine a regular site visit program to institutions covered by multiple project assurances, since other institutions may not even have an IRB in existence much of the time.

[16] If three-person teams were used, the cost of the program would increase to $350,000-$455,000 (assuming $625 per visit for the third person).

[17] The cost of FDA's inspection program in FY 1981 at 358 institutions came to approximately $400,000. FDA estimates that perhaps as many as one-fourth of their site visits are at institutions on the OPRR list.

[18] Letter from Charles McCarthy, Director, OPRR, NIH, to Bradford H. Gray (Nov. 19, 1982).

contracts was $2.9 billion, with research involving human subjects comprising roughly half that amount.[19] The average annual NIH grant in 1982 was $110,000-$120,000.[20] Thus, the cost of a site visit program would be the equivalent of two to three average NIH research grants per year. NIH awarded approximately 15,700 new and continuing grants in FY 1982.[21] It may be appropriate, therefore, to consider the cost of the site visit program in light of its purpose: to serve Congress's intent to ensure that the billions of Federal research dollars spent support ethical research that protects the interests of research subjects.

Additional Considerations Regarding Establishment of an IRB Site Visit Program

The feasibility of the approach developed by the Commission depends upon the participation of experienced IRB personnel as site visitors. It seems likely that the more the visits emphasize regulatory conformity, the less willing such persons will be to participate. Clearly, in establishing a program careful attention should be paid to establishing a good balance between regulatory oversight and collegial education.

Attention should also be given to the basis for selecting institutions for visits and to the frequency of visits. The Commission's site visits, though not at randomly selected institutions, found that procedural problems exist both at large institutions (that have sometimes developed inappropriate methods for increasing their efficiency) and at small institutions (that may have developed faulty procedures either because of relative isolation or because so little research is reviewed that insufficient thought has been given to the IRB's activities). Similarly, on the basis of its inspection visits, FDA found that IRBs on the NIH list (which presumably tend to be among the larger research institutions) often have problems that need correction.[22] Thus, it appears that institutional size provides no basis for assumptions about which institutions most need site visits. Since so much more research is reviewed at large institutions than at small ones, any selection bias that is contemplated should perhaps place emphasis on the large institutions. OPRR may have a more rational basis for determining the order in which institutions are visited after its new method of recording and analyzing the negative comments made in study section reviews is fully operational. Existing programs examined by the Commission suggest that a reason-

[19] *Id.*

[20] Figures provided by telephone by the NIH Office of Public Information, Nov. 1982.

[21] *Id.*

[22] Transcript of *IRB Compliance Activity Workshop* held by FDA in Washington (Nov. 7, 1980) at 21.

able initial goal would be to visit IRBs approximately every three to four years, with more frequent visits to institutions where serious problems are found.

Finally, a new site visit program should include explicit provisions for periodic evaluation of the program itself, both to improve the process over time and to determine whether the level of effort being devoted to the program is appropriate. It is possible that the problems that now exist in IRBs are sufficiently important that efforts should be made to complete initial site visits in less than three years. It is also possible that after a round or two of site visits, the need for continuing site visits will lessen and the frequency of site visits can be decreased; in this vein, FDA reports that investigators find significantly fewer problems on second inspections of IRBs than on first ones.[23] These are all options for which plans should be made at the outset of a site visit program for IRBs.

[23] *Id.* at 19, 23.

Recommendations

III

Conclusions and Recommendations

6

Based upon its hearings and studies during the past year, the Commission concludes that the implementation of the regulations governing research with human subjects could be improved. Some improvements in the regulations were recommended last year but have yet to be implemented. Other changes are needed to increase Federal agencies' knowledge of the implementation of their regulations by IRBs and to provide IRBs with information that will enhance their functioning.

Improving the Adequacy and Uniformity of Federal Laws and Regulations for the Protection of Human Subjects

(1) Congressional committees with oversight responsibilities for biomedical and behavioral research should monitor the progress of the administrative agencies in responding to the recommendations of the Commission's 1981 and 1982 reports on Protecting Human Subjects.

Comment. In its 1981 report on *Protecting Human Subjects*, the President's Commission made a number of recommendations including one that HHS act promptly to respond to the recommendations of the National Commission for the Protection of Human Subjects for special rules on research with children and with the mentally disabled. That report was transmitted to HHS Secretary Schweiker on December 30, 1981. Under the statute creating the President's Commission, the Secretary had 60 days (until March 1, 1982) in which to publish the report in the Federal Register; the report was published by HHS on March 29, 1982, on behalf of all affected agencies. A response in the form of proposed rules designed to implement the Commission's recommendations, or an explanation of the reasons for rejecting the recommendations, was

required under the statute within 180 days (September 27, 1982). An additional six months have now elapsed without an administrative response. The Commission remains hopeful that the ad hoc interagency committee that has been reviewing this subject for many months will soon arrive at a policy that implements the Commission's recommendations. Nevertheless, past experience with administrative delays on human subjects regulations suggests that, after the Commission's termination on March 31, 1983, congressional oversight may be needed to prompt the response from the Executive Branch required by the statute.

The fate of several recommendations of this Commission's predecessor, the National Commission for the Protection of Human Subjects, is illustrative. Over five years have now elapsed since the Department of Health, Education, and Welfare (now HHS) received recommendations on research involving children, and over four and one-half years have passed since it received recommendations for research involving the mentally disabled. The statute establishing the National Commission required timely publication and response by the Department to that Commission's recommendations. Because it was concerned by the inaction of the HHS, the President's Commission, in its First Biennial Report a year ago, called on the Department to act, one way or the other. As this Report was going to press, regulations governing research with children, approved by Secretary Schweiker on February 3, 1983, were cleared by the Office of Management and Budget and printed in the March 8, 1983, Federal Register, effective June 6, 1983. It appears that no action on the special provisions for research with the mentally disabled can be expected in the foreseeable future.

(2) An Ethics Advisory Board should be reestablished within the Department of HHS either through Congressional action, as part of the authorization of the NIH and ADAMHA research programs, or by the HHS Secretary.

Comment. The Commission has identified a number of ethical issues related to research with human subjects that deserve careful consideration by a national body composed of scientists, ethicists, lawyers, scholars in other relevant fields, and representatives of the public. Other problems are likely to emerge from time to time, as well. If this Commission no longer exists, there will be no forum in which such issues can be discussed and resolved in public by a group of individuals qualified by background and experience to provide sound guidance for administrative action. A properly constituted Board would also enhance public confidence that ethical issues of biomedical and behavioral research are receiving careful consideration.

Moreover, even if the Commission or other public body, or an all-government body (such as a Federal Coordinating Committee on Protecting Human Subjects), were in existence, there would still be need for an Ethics Advisory Board (EAB). The Commission and similar bodies are created to scrutinize issues of general policy, not to review individual research protocols. An EAB that would be available for prompt review of individual research proposals raising special problems concerning the protection of human subjects could be created by either legislative or executive action.

Under existing HHS regulations, certain types of research proposals must undergo review by an EAB before the Secretary may release funds for their support. Such a Board existed from 1978 to 1980; it was disbanded shortly after the Commission began its work in January 1980. Without such a board in place, unfortunate delays may be created in the processing of research proposals requiring EAB review, as was the case with the proposal submitted by Pierre Soupart in 1977 for support of research involving human *in vitro* fertilization. The Department was unable to act on that proposal for a year and a half because it had not yet established the Ethics Advisory Board.

A second issue concerns the EAB's membership and powers. HHS regulations provide only the bare outlines of these; more details could be supplied through a Congressional charter. It would be particularly advisable to require that HHS act on the EAB's recommendations within a specified time. The Commission notes in this regard that the report of the EAB on Dr. Soupart's request for research support, which was submitted to the Secretary, HEW, in May 1979, has yet to be acted upon. Sadly, Dr. Soupart has since died without ever having received a formal response to his application.

(3) Federal agencies should clarify the meaning of certain procedural requirements of present regulations, particularly what is meant by "IRB review."

Comment. The Commission's site visit project showed that "IRB review" at one institution may entail a careful discussion in a committee meeting, while at another institution it may mean that the protocol or similar document may actually be scrutinized by as few as two "primary" reviewers, with the IRB's role being confined largely to ratification of the decisions of these individual reviewers.

The present regulations state clearly that IRBs must review proposed research at convened meetings. If the purpose of this requirement is to ensure that protocols are actually examined and discussed by the full range of members required to be represented on an IRB, in order to permit all issues to emerge and be resolved through group processes, then practices at some institutions are thwarting that purpose. If the purpose is merely to generate a formal record that the group

met and approved a research project, then an IRB process relying on primary reviewers is not unacceptable.

Thus, the purpose of the regulations should be made clear on this issue. Such clarification will not necessarily require that Federal regulations be revised. Rather, HHS and the other affected Federal agencies could develop and disseminate information on "good committee practices." At a minimum it should be emphasized that the purpose of the IRB meeting is to have substantive discussion, not simply to ratify decisions made elsewhere. The Commission believes that research proposals and related materials should be distributed to all committee members (not just to primary reviewers) in advance of meetings.

Improving the Implementation of the Regulations

Congress specifically directed the Commission's attention to the need to ensure the adequacy and uniformity of the *implementation* of Federal regulations to protect human subjects as well as of the regulations themselves. The Commission's 1981 report, *Protecting Human Subjects*, recommended that existing duplication and variation among Federal rules for the protection of human subjects be eliminated. In the same spirit, the Commission believes that Federal implementation of the rules should be as uniform as possible, and, particularly, that steps to ensure that Federal monitoring of institutional implementation should be coordinated to minimize the burden imposed on institutions.

As described in Chapter Five, Federal agencies now use widely differing approaches to monitor the implementation of their rules by research institutions. For example, in administering the HHS regulations, the Office for Protection from Research Risks (OPRR) relies primarily on the written "assurances" in which institutions describe their IRBs and the steps they will take to comply with the regulations; OPRR also obtains some information as a result of NIH review of protocols that have passed through the IRB process and are awaiting Federal funding. The Food and Drug Administration (FDA), on the other hand, assesses regulatory compliance by means of visits to IRBs by field investigators and retrospective examination of the process as it was applied to research projects that are reported by sponsors to have received IRB approval.

The Commission believes that both advance assurances and on-site evaluations are needed. The assurance procedure provides a means of identifying certain problems and correcting them before research is conducted. In addition, the process of writing out an IRB assurance can be valuable for an institution by causing it to consider carefully its policies and procedures for IRB review. However, the assurance process

provides only a limited indication of how an IRB will actually work. Many aspects of an IRB's procedure are not covered in assurances; more important, a wide gap may open between the written assurance and the actual operation of the IRB.

The value of site visits lies in the opportunity they provide for the agency to learn how IRBs are actually functioning and for institutions to receive feedback on their IRBs' performance. However, to rely solely on after-the-fact site visits to determine whether an IRB meets basic regulatory requirements is to permit research to be conducted without knowing whether it has been reviewed by a properly constituted and procedurally sound IRB. Not surprisingly, it is difficult to apply a sanction for poor performance when the sanction is severe (disapproval of research results) and harms the sponsor (who probably relied on the IRB in good faith) rather than the wayward IRB. The Commission has concluded, therefore, that an adequate assessment by Federal agencies of the implementation of their rules for the protection of human subjects should incorporate both an assurance mechanism and site visits.

The Commission also concludes that if each affected Federal agency has its own system of reviewing assurances and visiting institutions to ensure that public funds are properly expended, the result would be duplicative, wasteful, and unduly burdensome to institutions. The following recommendations are designed to minimize this problem while providing the benefits of using both an assurance procedure and site visits to assure the effective performance of IRBs.

(4) A uniform system for implementing all Federal rules to protect human subjects should be established under a single office, and should include both assurances of regulatory compliance provided in advance by research institutions and periodic site visits to the institutions. Federal agencies that do not already do so should, as soon as practicable, identify the IRBs responsible for the initial and continuing review of research for which they have regulatory authority.

Comment. The Commission's 1981 report, *Protecting Human Subjects*, reviewed the need for uniformity of Federal rules for the protection of human subjects and made recommendations to accomplish this. Through the work of the interagency Ad Hoc Committee for Protecting Human Subjects, a mechanism is being developed for ongoing coordination of the rules. A similar mechanism is needed for coordination and simplification of the implementation of the rules.

Several departments and agencies now conduct inspections of IRBs to assess regulatory compliance, and some others apparently plan to do so. Other agencies rely on the supposed adequacy of the process used by HHS to administer its human subjects regulations—a process that does not now routinely include site visits to IRBs. The Commission has been informed

that HHS is actively considering development of a program of periodic visits to IRBs by site visit teams,[1] but such a program does not yet exist.

A combined approach, which includes both a prospective assurance mechanism and retrospective site visits, is needed. This will permit Federal agencies to know that the IRBs that are actively reviewing research are properly constituted and procedurally sound and that they are functioning properly.[2]

Recommendation (4) also calls for agencies to require identification of the IRB that reviews research covered by its regulations. The sponsor or supporter of research should know in advance what IRB is responsible for reviewing its research and that the IRB meets regulatory requirements. Private research sponsors sometimes seek this information from the FDA on an *ad hoc* basis—even requesting an inspection of an IRB to certify its acceptability for FDA-regulated research. A simpler and more consistent program would be for all IRBs to submit the necessary information for an assurance in advance. NIH, for example, requires that grant applications be accompanied by a form identifying the IRB that approved the study; similarly, the sponsors of research regulated by FDA should have such information available and should be able to provide it to FDA. Agencies (such as the FDA) that do not know which IRBs are reviewing the research covered by its regulations face serious difficulties in transmitting important information to IRBs, in rationally targeting a program of systematic site visits to institutions (*e.g.*, by attempting to visit new IRBs within the first year of their existence), and in answering basic inquiries about the IRBs that exist under its regulations (such as how many IRBs are there).

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[1] Testimony of Charles R. McCarthy, HHS Liaison to the Commission, transcripts of 2nd Meeting of the President's Commission (May 16, 1980) at 88-89, 14th Meeting of the President's Commission (Nov. 14, 1981) at 314-16, 334-35, 15th Meeting of the President's Commission (Dec. 11, 1981) at 86A-87A, 92A-93A, and 24th Meeting of the President's Commission (Sept. 11, 1982) at 361, 410-12; *see also*, letter from Charles R. McCarthy to Bradford H. Gray (Nov. 19, 1982).

[2] The Commission believes that institutions should be encouraged to go through the process of obtaining a "multiple project" or "general" assurance of compliance. However, it is likely that some research that is subject to Federal regulations will continue to be conducted at institutions where only a single project exists. For such institutions an assurance process along the lines of the "single project" or "special" assurances negotiated by OPRR may continue to be efficient and appropriate. It is probably not cost-effective to attempt to include such institutions in a site visit program of the sort that the Commission recommends. For such IRBs, the FDA inspection program will continue to play a useful role by keeping sponsors and investigators on notice that noncompliance may be detected.

(5) The prospective review of institutional assurances of compliance with applicable regulations should consider the amount and types of research that each IRB anticipates reviewing and should determine that requirements regarding IRB composition are met, that sound procedures have been established for the IRB's review of the research, and that the institution understands its responsibilities for protecting human subjects.

Comment. Since adoption of new HHS regulations in 1981, OPRR has been negotiating new assurances of compliance with more than 450 institutions, including virtually all institutions that conduct a large amount of research involving human subjects. The Commission does not intend that this process should be repeated to comply with Recommendation (5). However, since OPRR has a well-established program for negotiating advance assurances of compliance, and since most research institutions are likely to have occasion to negotiate new assurances with OPRR at some future time, the Commission believes that it is important to identify the elements of a sound approach to the advance review of institutional compliance with the regulations. Some have been a part of OPRR's past procedures; others have not.

The composition of an IRB should be examined to determine both whether it satisfies regulatory requirements and whether it is adequate in light of the types of research to be reviewed by the IRB. OPRR has well-established methods for these purposes.

The IRB procedures that should be reviewed in addition to those now reviewed by OPRR (such as provisions for continuing review and for recordkeeping), are those that are revealed by a description of the flow of paper and division of labor. Examples include: (1) what information is submitted for review by investigators (*e.g.*, entire protocols or summaries), (2) what information is distributed to all IRB members, (3) what review activities take place prior to or outside of IRB meetings, (4) what the procedures are for notifying investigators about needed changes.

OPRR has in the past encouraged institutions to follow a detailed "model" assurance; in the Commission's view, the advantages of this approach are outweighed by a major disadvantage—it enables institutions to come into regulatory compliance without giving serious thought to the full range of the IRB's tasks and responsibilities. It would be preferable to have institutions prepare their own statement of the IRB's responsibilities and the manner in which these will be met or to have institutions respond to a series of questions about how they propose to satisfy the various regulatory requirements.

(6) A broad educational and monitoring program covering the protection of human subjects and designed to reach

investigators, IRB members, research administrators should be conducted. Among the various activities included in the program should be site visits of research institutions using experienced IRB members and staff as site visitors.

Comment. The Commission is aware of the recently initiated NIH-FDA regional education program and supports the further development of audiovisual aids, self-instructional techniques, and self-evaluation guides for the education of those who have responsibility for protecting the rights and welfare of human subjects.

Among educational techniques for persons with responsibility for the protection of human subjects, the Commission finds the kind of site visits described in Chapter Four of this Report to be particularly helpful and effective. Although based on a small number of IRBs, the results of the Commission's site visit project, like the earlier study of IRBs by the National Commission for the Protection of Human Subjects, suggest that there is great variability among IRBs in their review procedures and interpretations of the regulations. This result is not entirely unexpected in view of the diversity and autonomy of IRBs. However, there is room for improvement in the way some IRBs function.

Because of the difficult judgments IRBs must make and the complex relationship between the performance of an IRB and its composition and procedures, the Commission believes that the functioning of an IRB can best be evaluated by persons who are knowledgeable about and experienced with the work of IRBs. Many IRBs would benefit from receiving knowledgeable feedback about their performance, and suggestions for improvements seem most likely to be accepted by an IRB if they are made by site visitors who are regarded as peers (*i.e.*, experienced IRB members or staff), perhaps accompanied by a staff member from the agency under whose auspices the visits are conducted.

The Commission is aware that site visits require an expenditure of money and time, both by Federal agencies and by research institutions. The Commission urges all agencies, notably OPRR and FDA, to consider budgeting funds already available for education and compliance activities to carry out more site visits of randomly selected institutions. FDA should carefully consider whether the resources it devotes to IRB inspections at institutions having assurances of compliance with OPRR could be made available for a coordinated site visit program, and whether FDA could deem those IRBs to have complied with FDA regulations. Many institutions have sent representatives to the recently instituted regional symposia and workshops. However, a significant number of investigators, IRB members, administrators, and staff could be better

informed concerning their responsibilities to human research subjects.

Site visits can reach many people who do not attend regional education programs and, if sensitively conducted, the site visit can identify specific strengths and shortcomings of an institution's procedures for the protection of human subjects without threatening the institution or intruding unnecessarily in its internal affairs. Therefore the Commission endorses site visits as a valuable aspect of the educational and monitoring effort of Federal agencies.

The Commission suggests that many of the lessons learned in its own site visit project and discussed in this Report should be considered in determining the kind of program to adopt. Among these lessons, the Commission draws particular attention to the following:

- That useful information can be derived from interviews (with IRB members, IRB staff, and investigators), from a review of records (particularly institutional procedures, IRB minutes, IRB project files, and consent forms), and especially from attending IRB meetings.
- That it is important for Federal agencies to assure regulatory compliance, but an excessive emphasis on regulatory conformity will reduce the value of site visits as an educational tool and make it more difficult to recruit suitable site visitors from outside of government.
- That IRB site visits of one day duration can provide visitors with a firm basis for identifying problems and offering suggestions; in some instances a one-and-a-half day visit may be preferable.

Care should be taken in planning site visits to consider the size and type of the institution, the nature of the research, the history of the IRB, and other matters that make each situation unique.

For reasons discussed in Chapter Five, it appears that a program of site visits might best be organized by the Federal office with coordinating responsibilities, which will probably be the Office for Protection from Research Risks at NIH. Private accreditation bodies have developed considerable relevant experience, however, and some mixture of governmental and private activity might have advantages.

In summary, cost, administrative efficiency, regulatory needs, and public accountability will all need to be considered by the Federal agencies in determining what kind of a program to establish.

Charter of the Federal Ad Hoc Committee for Protection of Human Research Subjects

A

Research involving human research subjects plays an essential role in combating disease and increasing knowledge. Only through research can proven advances be made in the prevention and care of disease and the relief of suffering. It is of critical importance to the public, the participants and to the scientific community that research activities be carried out without needless risk or distress and with the willing and enlightened cooperation of the human subjects involved in research.

For more than two years the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has been reviewing the policies and practices of Federal agencies which conduct, support or regulate research involving human subjects. It has issued its *First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Subjects in Biomedical and Behavioral Research.*

Affected Federal Agencies are required by Public Law 95-622 to respond to the recommendations of the President's Commission within 180 days after publication in the *Federal Register*. The Commission submitted its report to the President on December 31, 1981, and the report was published in the *Federal Register* on March 29, 1982.

Purpose

The *Ad Hoc* Committee is established to develop coordinated responses to the recommendations of the President's Commission contained in its First Biennial Report and to consider other issues pertaining to the protection of human subjects involved in research. Under Section 1802(b) of the Public Health Service Act as amended by Public Law 95-622, each Federal Agency that conducts, supports or regulates

research involving human subjects is required to undertake the recommended action or publish its determination not to do so in the *Federal Register* (with an adequate statement of the reasons for the determination).

Organization of the Committee

The Chairman of the *Ad Hoc* Committee for the Protection of Human Research Subjects will be the Assistant Secretary for Health, Department of Health and Human Services.

Represented Departments/Agencies/Commissions will be:

Agency for International Development
• Central Intelligence Agency
Consumer Product Safety Commission
Department of Agriculture
Department of Commerce
Department of Defense
Department of Education
Department of Energy
Department of Health and Human Services
Department of Housing and Urban Development
Department of the Interior
Department of Justice
Department of State (Ex Officio)
Department of Transportation
Environmental Protection Agency
National Aeronautics and Space Administration
National Science Foundation
Office of Management and Budget (Ex Officio)
Office of Science and Technology Policy (Ex Officio)
President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (Ex Officio)
Veterans Administration

Compensation

All members will be Federal employees who are allowed reimbursement for travel expenses by their agencies plus per diem for subsistence while serving away from their duty stations in accordance with Standard Government Travel Regulations.

Annual Cost Estimates

Estimated annual cost of operating the Committee, excluding staff support, is $1,000. Estimated cost of staff support, to be supplied by the Office for Protection from Research Risks, Office of the Director, National Institutes of Health is 3/4 person year at $30,000.

Reports

The Committee shall prepare a report for the Chairperson of FCCSET, and for each Agency Head when it completes it assigned task. The report shall contain at a minimum the Committee's functions, a list of members and their business addresses, dates and places of meetings, and a summary of the Committee's activities and recommendations.

Termination

Unless specifically extended, this Charter will expire February 28, 1983.

Determination

I hereby determine that the formation of the *Ad Hoc* Committee for Protection of Human Subjects is in the public interest in connection with the performance of duties imposed on the Executive Branch by law and that duties can best be performed with the advice and counsel of such a group.

(signed by)

Approved:_____

G.A. Keyworth

Chairman

Federal Coordinating Council for

Science, Engineering, and Technology

Date: May 25, 1982

Correspondence with the Assistant Secretary, HHS, on Responding to Reports of Misconduct in Biomedical Research

B

The material in this Appendix responds to questions initially submitted by the Commission to HHS Secretary Patricia Harris on September 18, 1980, concerning the meaning of, and existing procedures and plans for enforcing, the Department's regulations on "material failure" to comply with rules on the protection of human subjects. The Commission's questions were the subject of further conversations and correspondence between the Commission and officials of the Department.

On April 15, 1981, Richard Schweiker, Secretary Harris' successor, wrote to the Commission that no real standards could be promulgated because the way a case would be handled "depends upon the facts of a particular case." At a meeting on December 3, 1981, between Secretary Schweiker, the Assistant Secretaries for Health and for Policy and Planning, and the Commission's chairman and senior staff, the Secretary asked the Assistant Secretary for Planning and Evaluation to coordinate the Department's response to the Commission's continuing concern over the Department's policies and procedures for responding to reports of misconduct in biomedical research.

Documentation of the conversations and correspondence between the Commission and officials of the Department on this matter are set forth in Appendix F to the First Biennial Report, *Protecting Human Subjects*.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

FEB 16 1983

Morris B. Abram, Chairman
The President's Commission for the Study
of Ethical Problems in Medicine and
Biomedical and Behavioral Research
Suite 555
200 K Street, N.W.
Washington, D.C. 20006

Dear Chairman Abram:

Some time ago, you met with Secretary Schweiker to discuss several issues concerning the protection of human subjects. The enclosed responses to the questions you asked are set within a broader context: the general principles which govern this Department's approach to protecting human subjects of research, and the still-limited experience we have had with specific cases or applications of these principles to date.

The National Institutes of Health and other components of this Department are continuing to assess and consider responses to these and the related but broader problems of research misconduct. For example, review is focusing on such issues as protection of research animals, falsification of data, use of ineligible patients, and the responsibilities an institution or principle investigator has for overseeing staff actions.

Department staff were pleased by the finding of the Commission's recent study, Compensating Research Victims, which indicates "the evidence consistently suggests that the incidence of serious injury [to research subjects] is small...." However, these issues continue to be of significant concern. As Secretary Schweiker notified you previously, a task force has been established within HHS to consider the Commission's recommendations regarding compensation.

The Department has made significant progress in assessing these issues and in developing improved methods for dealing with them. I would expect that as the Department and others continue to review these issues, and as greater "case experience" is gained, the clarity and specificity of procedures will continue to improve.

Sincerely,

Robert J. Rubin, M.D.
Assistant Secretary for
Planning and Evaluation

Enclosure

HHS Responses to Questions Raised on Human Subjects Enforcement Procedures by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

Introduction

In biomedical science, ethical concepts and application as they affect the protection of human subjects of research are still in early stages. If the boundaries between societally acceptable and unacceptable activities in the area are not always clearly set, if we sometimes appear unsure how to operationalize, or are tentative in the application of, commonly held ethical principles to biomedicine -- these reflect the fact that our understanding of the underlying science and its implications is itself often imperfect. To assist in furthering consensus about, and in refining the principles for applying ethical standards to, developing areas of biomedical science have been major purposes of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research as they were for the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research which preceded it.

The National Commission and the Department of Health and Human Services (HHS) have devoted substantial effort to establishment of components of a process with sufficient flexibility to respond, often on an ad hoc basis, to a rapidly changing science base which affects research involving human subjects. In this process, the keystone, jointly fixed upon by the National Commission and the Department, has been the Institutional Review Board (IRB). It has been the Department's position that IRBs, local entities working within the broad framework and mandate established at 45 CFR 46, are best able to provide initial and on-going review of research affecting human subjects. The purpose of such review and monitoring is to assure that human research subjects are maximally protected from unnecessary risk, and that remaining irreducible risks are justified by the benefits of the research from which they stem.

While the Department has resisted those who would view IRBs as having police powers to enforce their determinations, the institutions within which IRBs are situated must provide assurances that compliance with the regulations will be maintained. The National Commission and the Department have agreed that IRBs are simply the agents institutions must establish to undertake, as a minimum, the requirements of 45 CFR 46. An institution is free to give to its IRB a charge broader than that required by 45 CFR 46, but the institution is the entity ultimately held responsible under the regulation for

assurring the protection of human subject from inappropriate research risks.

Under 45 CFR 46, an IRB shall at least:

- review to assure the minimization of risk to subjects, and have authority to approve, require the modification of, or disapprove, all research subject to the regulation;
- determine whether, for particular research, information in addition to that required by the regulation is necessary to assure the informed consent of research subjects, and require the provision of such information;
- carry out on-going review of research in accord with the regulations, with authority to suspend or terminate such research if found out of compliance with IRB requirements, or resulting in unexpected harm to subjects; and
- notify the investigator, appropriate institutional officials, and the Secretary should suspension or termination of research be necessary.

In sum, the Department believes that responsibility for determining the nature and extent of risk, design of specific procedures to minimize such risk, on-going review and followup to assure achievement of minimization of risks, and, where necessary, suspension or termination of unacceptable research, lies first and foremost with the institution and IRB. Through 45 CFR 46, IRBs and institutions have been provided the authority necessary to implement this responsibility.

However, the Department also recognizes its own accountability and oversight responsibilities in assuring protection of human subjects. This responsibility encompasses such areas of concern as the functioning of IRBs and effective involvement of institutions.

Background

In assessing issues raised by the President's Commission and in development of its response, the Department has held several principles to be of paramount importance.

- Institutions should be required to investigate and report their findings to Department officials in all matters pertaining to alledged noncompliance with 45 CFR 46 policies and requirements.
- Within HHS, development of information, conduct of necessary investigations, and initiation of follow-up

actions should be the responsibility primarily of the pertinent Operating Divisions (OPDIVs) of the Department, not the Office of the Secretary (OS).

There is some theoretical appeal to centralizing responsibility for receipt of complaints, conduct of investigations, and, where appropriate, imposition of subsequent sanctions in OS. Such centralization would appear to improve control and accountability. The Department believes, however, that the costs associated with such centralization substantially outweigh these apparent benefits. Three factors stand out.

First, specialized scientific knowledge is frequently as necessary to the initial screening of a complaint, to determine whether further investigation is warranted, as in the investigation itself. Second, potential informants or "whistle blowers" are more likely to approach familiar OPDIV contacts, whom they frequently meet for other purposes, than unknown representatives in OS, a distant central Department office. Third, the willingness of OPDIV staff to informally communicate to research community peers an interest in knowing of possible problems is likely maximized by placing primary responsibility on the OPDIVs. Put directly, if OPDIVs lack responsibility to act, their incentive to care may be substantially lessened.

Not only are the Department's OS staff offices poorly equipped to take on responsibility for grantee conformance to regulations for the protection of human subjects, but also, more importantly, to build that competence would be costly and inefficient, while still not being as productive of information as using the less formal peer network already in place. Again, if responsibility is pulled into the Office of the Secretary, the interest and concern now extant among OPDIV staffs would likely be seriously diminished. However, maintaining primary responsibility for development of information, conduct of necessary investigations, and initiation of follow-up actions in the OPDIVs, focused in the NIH Office of Protection from Research Risks (OPRR) does not rule out the participation of staff offices as appropriate -- including an OPDIV's request for such participation. By reserving to the Secretary and his office a review and approval function, the Department believes most of the benefits which flow from centralization can be had concurrent with those of decentralization.

. There is of necessity a delicate balance between preserving discretion and the need for established rules, and due process for the investigator. In that balance, however, the Department believes that protecting human subjects should be the dominant consideration.

There is a natural tension between the twin goals of establishing a regularized, standardized approach and maintaining maximum flexibility for the Department. Establishment of procedures, an ordered hiearchy of penalties and complete definition of terms, assures an unambiguous system and provides a check on possible Department laxity or misfeasance. A totally routinized and unambiguous system, however, by definition limits the discretion and flexibility necessary to respond most appropriately to unanticipated, new, or unique circumstances.

The rapidity and range of recent progress in biomedical sciences is unprecedented. Development and application of lasers, hybridoma and recombinant DNA products, and heart and lung replacements are simply symptomatic of vast change and movement in science. The implications such progress has for research subjects may be vast.

The 45 CFR 46 regulation was drafted to preserve necessary flexibility, through which to protect research subjects within a shifting base of scientific research. The regulation is unusual if not unique in that it covers all research involving human subjects except that specifically excluded, an implicit recognition of the dramatically changing state of science. Built into the regulation is a method for expanding the research exempted from, or subject to "expedited review" under 45 CFR 46. As increased experience has been gained by the scientific community and the Department regarding activities which do not seem to pose a significant danger, the scope of excluded research has been increased. Additional areas within which "expedited review" is permissible or for which total exemption is appropriate, may be defined as experience is increased.

. While the paramount objective is to protect subjects, insofar as possible this must be done without prejudging investigators.

The Department believes that sufficient flexibility must be preserved to permit those actions necessary to swiftly protect subjects of research from harm. In some instances, such intervention may even precede the launching of a thorough, detailed investigation. In other cases, this may mean that intervention is necesary before a detailed investigation has been completed. Accompanying the ability to rapidly intervene, however, is an obligation upon those who intercede, whether representative of the Department, the institution, or the IRB, to do so only to the extent necessary, and then in such fashion as to protect the rights and reputations of participant researchers. This obligation is particularly strong when intervention may be undertaken based on interim findings prior to completion of a full, thorough and detailed investigation.

Questions Raised by the President's Commission

A. What constitutes "material failure" by an investigator or institution to protect human subjects? What standard of proof does the Department require for a finding of "material failure"?

Although use of the term "materially failed" [45 CFR 46.123] leaves room for administrative discretion, it was intentionally chosen to require an affirmative finding of seriousness-in-fact before early termination of research funding may be initiated. The standard was chosen to afford a measure of protection to institutions because insubstantial and minor violations would not provide the basis to terminate or suspend; rather, failures or violations must be determined to be sufficiently serious in nature to justify termination or suspension.

While the phrase insures exclusion of, for example, trivial procedural failures, it gives the Department sufficient latitude to consider a full variety of serious offenses, including such violations or offenses and the circumstances surrounding them that cannot be fully anticipated in advance.

B. What steps are taken to assure the protection of human subjects during the period when allegations of wrongdoing are being investigated?

The steps necessary to assure the protection of human subjects obviously depend upon the nature and content of the specific research protocol -- that is, the nature of possible risk to subjects -- about which allegations of wrongdoing or inadequate protection have been made. The speed and scope of intervention by the Department are likely to be affected by the degree and amount of risk posed to subjects. An alleged failure to secure signatures on the consent forms of a few research subjects would not bring about the same response as an alleged threat to the lives of all subjects of the research.

Experience to date has been too limited, and the theoretical range of potential cases is too broad, for the Department to respond beyond indicating that protective actions in specific cases have been, and will continue to be, taken on an ad hoc basis -- whenever possible in concert with the sponsoring institution.

It should be noted that experience supports the Department's presumption that researchers, the research community, IRBs and institutions within which the research is undertaken have a common interest with the Department in protecting human subjects from harm. That commonality of interest is grounded not only in positive common precepts about the moral and ethical

responsibilities; researchers and scientists are also subject to peer pressure and tort law.

C. What are the roles and authority among offices at NIH (OPRR, General Counsel, Division of Management Survey and Review, Associate Director for Extramural Research, Director-NIH) and between NIH and the Office of the Secretary in:

1. Deciding whether an investigation is required;

2. Conducting an investigation;

3. Determining whether to initiate debarment proceedings [this question element is repeated at D.2, below; the Department's response is provided there];

4. Notifying the Office of the Inspector General about problems requiring investigation or about findings of misconduct; and

5. Determining whether sanctions should be imposed and, if so, what sanctions to impose?

The Office for Protection from Research Risks (OPRR), a component of the Office of the Director, has the lead responsibility within the National Institutes of Health for virtually all aspects of human subjects' protection. In that role, OPRR has usually been the initial recipient of allegations, complaints, and expressions of concern made to the Department about specific research subject to 45 CFR 46. In instances where concern may have been expressed initially to other components of NIH or the Department, those components in turn notify OPRR. It also receives, on behalf of the Secretary, notification to the Department by IRBs and institutions of recommendations regarding research suspension or termination resulting from non-compliance with IRB requirements, or from unexpected harm to subjects.

In conducting its initial screening of complaints, OPRR is responsible for determining whether follow-up investigation, including the involvement of the cognizant institutional officials, is required (the institution is free to include the IRB); conducting such investigatory actions as may be necessary; summarizing results of investigations; and, based on such findings, recommending appropriate action. In executing these responsibilities, OPRR calls upon other components of NIH and the Department as necessary. Within its role as lead office, OPRR may ask, for example, for scientific, legal, or investigatory assistance. As appropriate, these requests may be either formal or informal in nature, as may be the provision by other components of the desired assistance.

Findings, conclusions, and recommendations made by OPRR following necessary investigations are subject first to the review of the Associate Director for Extramural Training and Research and, as necessary, through the Associate Director, subsequent reviews by the NIH Director, the Assistant Secretary for Health, and the Secretary. In urgent cases, such additional reviews may be undertaken concurrently. Similarly, as appropriate, other NIH and Department components will have been kept informed of progress during the various stages of OPRR's investigation.

D. What standards govern decisions to initiate proceedings for debarment or suspension:

1. Who makes the decision;

2. At what stage of an investigation is such a decision made;

3. What factors are taken into account in making the decision; and

4. May a principal investigator or grantee institution request debarment proceedings in order to invoke the hearing provisions?

Debarment is but one of several options available to the Department to deal with a wide variety of improper behaviors including, for example, failure to comply with program regulations or audit requirements. It applies only where offenses are especially serious (see below). To date, the debarment penalty has been exercised only once. In its single application, the harm to which human subjects were exposed was but one among a number of Department concerns regarding conduct of the research which led to debarment. Further, it should be noted that the investigator in question did not challenge the findings of fact upon which the debarment was based, nor application of the debarment sanction itself.

As review of the Notice of Proposed Rulemaking, the Department's exampling and general response to public comments on that rulemaking, and the Final Rule make clear, debarment is intended as a sanction appropriate only in the most serious cases of fraud and abuse by grantees or recipients of other forms of financial assistance. The Department recognized at the time of publication that the rule allows substantial administrative discretion. The Department argued then that such discretion was necessary to provide for "the myriad of situations which may arise. It is essential to handle unpredictable circumstances." (Federal Register, Vol. 45, No 198, October 9. 1980; page 67263.) The Department continues to hold to this position, as much of the preceding has indicated.

While claiming for itself discretion sufficient to meet unforeseen and unpredictable circumstances, the Department recognized in the Rule, and accepts in fact, that protection against abuse of such discretion is necessary and appropriate. Elements established within the rule, pertinent to possible debarment for reasons related to human subjects, and which assist in assuring that the Departmental discretion permitted is not abused include the following:

- "the existence of any of the cause set forth in Sec. 76.10 [causes for debarment] does not effectuate a debarment or necessarily require that an institution or individual be debarred" (Sec. 76.11);

- "mitigating factors, such as the degree of seriousness of the offense, violation, failure, or inadequacy of performance, will be considered in deciding whether debarment is warranted" (Sec. 76.11);

- individuals or instititutions must be informed that the Secretary is considering debarment, and are free to request a hearing, at which the individual or institution may be represented by counsel (Sec. 76.14);

- such hearings will be conducted by a hearing officer without prior involvement in the matter (Sec. 76.14), who shall make a determination on the evidence presented and record of findings (Sec. 76.15); and

- the determination of the hearing officer may be appealed to the Secretary (Sec. 76.15).

In sum, final authority to suspend or debar for human subjects' infractions under 45 CFR 46 is reserved exclusively to the Secretary. In exercising that authority, the Secretary will consider elements such as the degree and intentionality of risk, the gravity of harm to human subjects, and prior offenses against human subjects' and other regulations. It is virtually inconceivable that action to debar would be contemplated prior to completion of OPRR's investigation, and review of the findings of the investgation by levels up to the Secretary.

Given the regulation's implication that debarment is called for only under the most unusual and serious circumstances, we find it improbable that a grantee or institution would institute a request for Departmental initiation of debarment proceedings under 45 CFR 46. With regard to protection of human subjects, such circumstances would likely involve flagrant and/or intentional violations, threatening significant real harm to human subjects, and for which no mitigating explanation could be found.

One exception to the preceeding could stem from an investigator's or sponsoring institution's hope of speeding resolution by the Department of allegations brought under 45 CFR 46. The Department would not be in a position to act on such a request to initiate hearings prior to completion of investigations by the institution and/or OPRR, however. And, since independent of a grantee or investigator request, once such investigations had been completed, the Department would initiate appropriate actions, we believe this exception to be largely theoretical.

Finally, it is unlikely that institutions or grantees would wish to request initiation of debarment to invoke its hearing provisions to present additional or mitigating information. The development and investigation processes preceeding virtually all sanctions or actions which the Department might take at the agency, OPDIV, and Office of the Secretary levels with regard to 45 CFR 46 or other violations allow for formal and/or informal appeals and/or the consideration of additional information without the applicant having to invoke the debarment provisions.

Policy Statements on the Proper Conduct of Research

C

The Maintenance of High Ethical Standards in the Conduct of Research*

Foreword

In January 1982, the Association of American Medical Colleges appointed an *Ad Hoc* Committee on the Maintenance of High Ethical Standards in the Conduct of Research. The committee was chaired by Julius R. Krevans, M.D., Dean of the University of California, San Francisco. The decision to establish this committee resulted from concerns that the wide attention received by several instances of misconduct by biomedical investigators would call into question the integrity of the whole research enterprise.

The Association believes that faculties and their institutions have the primary responsibility to maintain high ethical standards in research and to investigate promptly and fairly when misconduct is alleged.

The committee report was adopted by the Executive Council on June 24, 1982, as a guide to faculties of the medical schools and teaching hospitals who are responsible for the integrity of the biomedical research enterprise.

John A.D. Cooper, M.D.
President
Association of American Medical Colleges

* Adopted by the Association of American Medical Colleges (June 24, 1982);

AAMC Ad Hoc Committee on the Maintenance of High Ethical Standards in the Conduct of Research

JULIUS R. KREVANS, M.D., *Chairman*, Dean, University of California, San Francisco, School of Medicine
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ROBERT HILL, Ph.D., Chairman, Department of Biochemistry, Duke University Medical Center
HAROLD HINES, President, Ryan Insurance Group
ARNOLD S. RELMAN, M.D., Editor, *New England Journal of Medicine*
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LEROY WALTERS, Ph.D., Director, Center for Bioethics, Kennedy Institute, Georgetown University

Introduction

The principles that govern scientific research have long been established and have been applied by faculties and administrators of academic medical centers and teaching hospitals for the discovery of the new knowledge that is needed to promote the health and welfare of mankind. The maintenance of high ethical standards in research based on these principles is a central and critical responsibility of faculties and administrators of academic medical centers. Recently, however, there have been a number of instances of misconduct, including fraud, in research and in reporting of research data which have received wide attention. Validity and accuracy in the collection and reporting of data are intrinsically essential to the scientific process; dishonesty in these endeavors runs counter to the very nature of research, that is, the pursuit truth.

The responsibility of the scientific community to the public is acknowledged. The maintenance of public trust in this pursuit is vital to the continuing vigor of the biomedical research enterprise. Loss of this trust because of isolated instances of dishonest behavior on the part of a few researchers could cause great harm by calling into question in the mind of the public the validity of all new knowledge and the integrity

of the scientific community at large. In short, it is in the best interest of the public and of academic medicine to prevent misconduct in research and to deal effectively and responsibly with instances where misconduct is suspected.

The primary goal of this document is to set forth guidelines and recommendations that will be useful to medical schools and teaching hospitals in designing their individual institutional approaches to dealing with alleged misconduct by researchers. Although the guidelines and recommendations that follow principally address fraud (i.e., the intentional fabrication, falsification, or "stealing" of research data) they may also be useful in institutional efforts to deal with the violation of existing administrative procedures and ethical codes for the treatment of human and animal subjects of research and other problems that may arise in the conduct of research.

The Prevention of Research Fraud

The primary responsibility for taking steps to prevent research fraud rests with the scientific community. In academic institutions, it can best be executed by the faculties. In a free society, and particularly in the academic milieu where creativity and individual thought are qualities to be fostered and not stifled, aberrant behavior of individuals cannot be completely controlled. It is unrealistic, therefore, to assume that research fraud can be entirely prevented. On the other hand, faculties can create a climate that promotes faithful attention to high ethical standards. This climate should enhance the research process and should not inhibit the productivity and creativity of scientists.

It is recognized that the principal deterrent in research fraud is the overwhelming probability that fraudulent data will be detected soon after their presentation. Virtually all experimentation leading to scientific findings of significance will be repeated, and the likelihood that falsified, fabricated, or plagiarized data will go unquestioned is exceedingly slim. Despite the self-correcting nature of science, however, instances of research fraud have occurred and faculties should explore additional measures to decrease further the likelihood that a researcher will risk the odds and commit fraud. Faculties and institutional officials should consider the following:

- Having in place a conspicuous and understandable mechanism for dealing with instances of alleged fraud.
- Adopting institutional policies that define misrepresentation of research data as a major breach of contract between the faculty or staff member and the institution. (This policy should particularly be articulated in the faculty handbook.)

- Articulating institutional policies that foster openness of research.
- Encouraging faculties to discuss research ethics to heighten awareness and recognition of these issues.
- Establishing institutional policies to provide: 1) an appropriate and clearly defined locus of responsibility for the conduct of research; 2) assurance that individuals charged with supervision of other researchers can realistically execute their responsibility; and 3) particular attention to adequate supervision of large research teams.
- Assuring that quality rather than quantity of research is emphasized as a criterion for the promotion of faculty.
- Examining institutional policies on authorship of papers and abstracts to ensure that named authors have had a genuine role in the research and accept responsibility for the quality of the work being reported.
- Reviewing institutional policies on the recording and retention of research data to ensure that such policies are appropriate and are clearly understood and complied with by all faculty.
- Examining the institutional role and policies in guiding faculty concerning public announcement and publication of research findings.

Institutional Responses to Instances of Alleged Research Fraud

As previously stated, it is highly advisable for faculties to have in place procedures to deal with reports of misconduct in order that alleged fraud can be investigated and resolved in an expeditious, thoughtful, fair, and judicious manner. Although it would be virtually impossible to anticipate in advance the precise course that all investigations and subsequent actions should take, procedures for handling initial reports of fraud should be established prospectively and all researchers should be cognizant of the existence of these procedures.

In developing policies and procedures, institutions and their faculties should recognize that judgments about the substantive questions relating to whether research findings are true or false must largely be made by faculty peers. If action adverse to a faculty member is taken by the institution based upon findings of fraud and such action is later challenged in court, the court ordinarily will look to see if fair procedures have been followed; that the accused had an adequate opportunity to explain and defend his actions, including when appropriate, confronting those persons who presented evidence of fraud; and that the decision was not arbitrary or capricious, but based on credible evidence. If institutional

policies and procedures meet these criteria the courts are unlikely to interfere with the institutional decision.

The following guidelines and procedures for dealing with allegations of fraud are offered as a prototype to assist schools in designing a process appropriate to their own situations. Consultations with university counsel in such an effort are strongly recommended. It is recognized that in these procedures a faculty member's reputation is put at risk during the investigation. This is justified since scientists on the university faculty occupy a special place of privilege and responsibility and must be held to a higher standard of conduct. The procedures indeed must be fair to the individuals involved. They must also be designed to be responsive to the special responsibility that science and faculty have to society.

Prototype of Procedures for Dealing with Alleged Research Fraud

Processing Initial Reports of Fraud

- From the outset, institutions should protect rights and reputations for all parties involved including the individual(s) who report perceived misconduct in good faith.
- Initial reports of alleged fraud should be brought to the attention of the faculty member responsible for the individual whose actions are in question. That person should in turn report the allegations to the department chairperson immediately.
- If the initial report of misconduct is not regarded as blatantly frivolous in nature, the report should promptly be referred to the dean or the chief executive officer of the institution. The dean should in turn immediately initiate a review by individuals at the institution who have been designated to review initial reports of fraud. Such individuals should be selected from among the faculty and administration. Care should be taken to exclude those with personal responsibility for the research under investigation.
- After this initial review, a determination should be made as to whether the report warrants more thorough investigation. If it is determined that there is sufficient basis for pursuing the allegations, the researcher(s) in question should be advised of the allegations and any collaborators should be informed of the pending investigation.

Investigation of Reported Fraud that Appears Substantial

- Institutions should have in place or be prepared to appoint immediately a committee or other administrative unit to conduct a prompt and thorough investigation of the reported fraud and should consider the

merits of involving outside, objective parties in the investigation at this stage.

- The sponsoring agency should be notified that there is an investigation underway.
- During the investigation, consideration should be given to the review of all research with which the individual is involved.
- The investigating committee or unit should determine whether there was fabrication or dishonesty.
- Throughout the investigation, the individual and any collaborators or supervisors whose role in the alleged misconduct is questionable should be advised of the progress of the investigation and be afforded the opportunity to respond and provide additional information.

Subsequent Action Following Completed Investigation

1. If the alleged fraud is substantiated by a thorough investigation the following actions are recommended:

- The sponsoring agency should be notified of the findings of the investigation and appropriate restitution should be made.
- All pending abstracts and papers emanating from the fraudulent research should be withdrawn and editors of journals in which previous abstracts and papers appeared should be notified.
- Institutions and sponsoring agencies with which the individual has been affiliated should be notified if there is reason to believe that the validity of previous research might be questionable.
- Appropriate action should be taken to terminate or alter the status of faculty members whose misconduct is substantiated.
- Institutional administrators should consider, in consultation with legal counsel, release of information about the incident to the public press, particularly when public funds were used in supporting the fraudulent research.

2. If the alleged fraud is not substantiated by a thorough investigation, formal efforts should be undertaken to restore fully the reputation of the researcher and others under investigation. In addition, appropriate action should be taken against any parties whose involvement in leveling unfounded charges was demonstrated to have been malicious or intentionally dishonest.

3. Subsequent to the completion of an investigation, faculty practices and institutional policies and procedures for promoting the ethical conduct of research and investigating

allegations of misconduct should be scrutinized and modified in light of the experience gained.

Conclusion

The foregoing are offered as guidelines around which faculties and their institutions can develop processes for promoting ethical standards in research and in dealing with misconduct and fraud. It must be emphasized that developing an appropriate process for detecting and responding to alleged fraud is sensitive and complex. Implementation of these policies and guidelines should not require the development of an elaborate, administrative bureaucracy. Simple, perfect, cut-and-dried procedures do not exist and to suggest that they do, ignores the difficulties inherent in achieving a balance between protecting the integrity of the research effort and protecting the rights of individuals.

Yale Policy Statement On Collaborative Research*

Preface to Yale University Policy Statement on Collaborative Research

To the dismay of the academic community and the public, recent instances have occurred at other universities and at Yale in which the product of scholarly research has been falsified or willfully adulterated. Academic fraud is not a new problem, and the world's institutions of scholarship have for centuries fought to purge their communities of instances of inauthenticity and plagiary. Today, however, academic fraud often has a new element: it arises out of collaborative research in circumstances in which some members of a research team relied upon and accepted as authentic the work of other members of the team, and were betrayed. In view of the importance of this subject, the President, on November 12, 1981, made the following statement:

> Recent incidents of inauthenticity and error in published accounts of some collaborative research performed at Yale have raised issues of serious and broad concern to the University. These larger issues transcend the facts of any particular case or of any particular School of the University. Pressures on scholars engaged in collaborative work and the overcommitment that often occurs thereby, can heighten the possibility that additional pressures and problems may occur in the process of collaborative work. At the request of the Corporation,

* Approved by the President and Fellows of Yale University (May 23, 1982); Weekly Bulletin and Calendar (September 13-20, 1982); reprinted with the express permission of Yale University.

therefore, the President will appoint a University-wide committee to examine these larger issues and concerns. The committee will recommend to the President and to the Fellows of the Corporation principles designed to lessen such pressures without infringing upon or predetermining the nature and direction of collaborative forms of scholarship.

The Committee given this charge was appointed under the chairmanship of Professor Jaroslav Pelikan* and, in February 1982, the Committee submitted its Report to the President. The Corporation expresses its thanks to the Committee for its work, upon which the Corporation has drawn in preparing the following statement of policy.

Yale University Policy Statement on Collaborative Research

I

The scholar works within an environment that has been developed for conducting, supporting, and evaluating scholarly research in the single-minded pursuit of truth. Our system, however, keeps all scholars, be they young investigators or established figures in the field, under considerable pressure. For those for whom the competitive pressure proves to be too great, this system can lead to intellectual rashness and lack of rigor and, occasionally, even to academic fraud.

Academic fraud is more than error; it may take the form of falsification or fabrication of data, plagiarism, or grossly negligent data collection or analysis. It is hardly possible to exaggerate the damage that can result from such a breach of the academic commitment to truth. Academic fraud, if discovered, as it often is, not only shatters individual careers, but besmirches the entire cause of objective research, undermines the credibility of scholarship and rends the fragile tissues of confidence between scholar and scholar, teacher and student, the university and the public.

Collaborative research, sometimes engaging numbers of investigators pursuing parts of an integrated project in different places, is a fact of modern academic life. Every indication is that the amount of such collaborative work will continue to

* The Committee members were Jaroslav Pelikan, Sterling Professor of History; Pierre Demarque, Munson Professor of Natural Philosophy and Astronomy; Joseph Goldstein, Sterling Professor of Law and Professor at the Child Study Center; George Palade, Professor and Chairman of the Department of Cell Biology; Albert J. Reiss, Jr., William Graham Sumner Professor of Sociology, Professor at the Institution for Social and Policy Studies and Lecturer of Law; Judith Rodin, Professor and Director of Graduate Studies in the Department of Psychology; Leon E. Rosenberg, Professor of Human Genetics and Pediatrics and Chairman of the Department of Human Genetics; and, Kenneth B. Wilberg, Whitehead Professor of Chemistry.

increase within this academic community, and between universities and other private and governmental institutions. We do not deem it appropriate to legislate detailed procedures for the conduct of collaborative research, for we believe that instances of dishonesty are rare. Regulation might well erode the freedom in the pursuit of knowledge we require and the atmosphere of mutual trust among colleagues and collaborators we cherish.

In collaborative research the iniquity of academic fraud is compounded, for the perpetrator not only clouds his own academic future, but inevitably clouds that of his research colleagues—at a minimum, depriving them of the benefit of their own hard work, and at worst, staining their reputations in the view of outsiders who do not take the trouble to distinguish between those collaborators who are guilty and those who are in fact victimized.

We do not view the seriousness of the offense in cases of fraud done in a collaborative context to be any different from the seriousness of offenses in the context of individual work. Indeed, joint authorship requires a heightened awareness of responsibility. When research is published under multiple authorship, each author claiming credit for the entire work, it must be self-evident that any fraud or inauthenticity in the work will taint all the authors. By claiming authorship of a scholarly publication, each collaborator must accept the discredit, as well as the credit, for the collaborative effort.

Common sense will dictate, and we endorse as a standard, that primary investigators in collaborative research projects should, in the interest of preserving the integrity of the group's research project, exercise care in selecting collaborators and make reasonable and periodic inquiry as to the integrity of the processes for gathering and evaluating data. Moreover, we trust that awareness of the implications of collaborative participation in research and scholarly publications and the statement of concern expressed herein will prompt individuals to consider appropriate changes in practice and custom that will reflect the different needs of different fields, departments and disciplines, while at the same time preserving the irreplaceable ideals of collaboration and collegiality that are necessary no matter which discipline is concerned.

Any form of intellectual inauthenticity and academic fraud must be condemned in the strongest possible terms. All scholars have an obligation to disclose what they believe in good faith to be well-founded suspicions of academic fraud. Allegations of fraud must, of course, be made with great caution; yet those who come forward with such allegations must understand that the University respects the honest exercise of their judgment. At the same time, the rights of those whose work product is questioned must also be scrupulously

protected, all in accord with a process that responds to such allegations with the utmost care, diligence, sensitivity, and respect for the rights of all concerned.

II

Yale University will adhere to the following procedure with regard to any instances of alleged academic fraud arising out of the performance of scholarly research. If it should appear that an incident of academic fraud may have occurred in this community:

1. The matter shall be reported immediately to the Dean of the School or faculty concerned.

2. If the Dean finds that in the circumstances the allegations are sufficiently plausible to warrant investigation, the Dean will (confidentially or with public announcement as his discretion may dictate) investigate the matter sufficiently to conclude whether or not there are reasonable grounds to believe that the allegations may be true.

3. If the Dean finds that there are no reasonable grounds to believe that the allegations may be true, he or she will terminate the inquiry into the matter.

4. If the Dean finds that there are reasonable grounds to believe that the allegations may be true and that, if proven, would warrant sanctions which are not severe, the Dean will pursue the matter in accordance with the disciplinary proceedings applicable to the School.

5. If, on the other hand, the Dean finds that there are reasonable grounds to believe that the allegations may be true and that, if proven, would warrant the imposition of severe sanctions, the Dean shall, in the case of the faculty, recommend to the President of the University that the University Tribunal be convoked to assume jurisdiction over the matter. In the case of students, the regular disciplinary procedures of the School shall apply, and in the case of staff, the matter shall be referred to the Provost or the Vice President for Finance and Administration, as appropriate, for action.

6. If the President decides to convoke the University Tribunal, the matter will be dealt with in accordance with the regular Procedures and Regulations of the University Tribunal, adopted by the Fellows of the Corporation in September, 1980.

7. In principle, any faculty member who personally engages in academic fraud, whether or not in collaborative research with others, or who accedes to the publication of work, any part of which he or she knows to have been falsified or adulterated or to be fraudulent, should, in the absence of extenuating circumstances, be dismissed from the University.

8. If academic fraud is found to have been committed by a collaborator other than the primary investigator, and the primary investigator is found not to have made reasonable and

periodic inquiry as to the authenticity of the work product of their collaboration, and if compliance with these standards would probably have prevented the fraudulent occurrence, the primary investigator should be subjected to censure or other appropriate sanction.

9. Whenever any instance of academic fraud is found to have been committed and the ensuing work published, announcement of the facts in the matter shall be promptly made in sufficient detail, in such form, and through such channels, as to inform the relevant academic and public communities and establish a correct public record.

HHS Proposals on Exemption of Social Policy Experiments from 45 CFR 46, and Commission Correspondence with the Secretary, HHS

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Federal Register / Vol. 47, No. 43 / Thursday, March 4, 1982

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

45 CFR Part 46

Waiver of Requirements as Applied to Medicaid Demonstration Projects Involving Cost-Sharing (Copayments, Deductibles, Coinsurance)

AGENCY: Office of the Secretary, HHS.

ACTION: Notice of waiver.

SUMMARY: The Department of Health and Human Services hereby gives notice that, pursuant to 45 CFR 46.101(e), the Secretary has decided to waive the requirements set forth in Part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost-sharing, such as deductibles, copayment and coinsurance, in the Medicaid program (Title XIX of the Social Security Act). The Secretary believes that waiver of Part 46 requirements is appropriate since it will facilitate the timely efficient operation of demonstration projects which are likely to assist in promoting the objectives of the Medicaid program.

DATE: Effective: March 4, 1982.

FOR FURTHER INFORMATION CONTACT: Steven Pelovitz, (301) 597-3195.

SUPPLEMENTARY INFORMATION:

The rapid escalation of Medicaid costs in recent years makes it imperative for the Department and the States to conduct research which would explore ways to provide optimum medical care while controlling costs that would otherwise make the program unaffordable. Provisions of the Omnibus Budget Reconciliation Act of 1981 (Pub. L. 97-35) which, beginning in Fiscal Year 1982, imposes certain new restrictions on the amount of Federal reimbursement which will be available to States for the Medicaid program, make it critical that this research proceed expeditiously. Cost-sharing demonstration projects are likely to be an important part of this research and, without a waiver of the Part 46 requirements, each otherwise approved project would have to go through the process of review by an Institutional Review Board (IRB) before it could be implemented.

Under Part 46, the primary functions of IRB review are to assure that the human subjects of research are not exposed to risk which is unreasonable in light of the benefit to be gained, and that their appropriate informed consent has been obtained (§ 46.111). However,

in the case of research conducted to study Federal or State benefit programs, such as a copayment or other cost-sharing demonstration projects, where participation of a large number of individuals would make it impractical to proceed if informed consent had to be obtained from each one, the provisions of Part 46 contemplate IRB waiver of the informed consent requirements. Further, in research such as a Medicaid cost-sharing demonstration project, the possibility of any risk arises solely from the modification of benefits or the means of obtaining benefits available through the governmental assistance program. Modifications of this nature are clearly authorized by, and inherent in the concept of demonstration projects conducted under section 1115. Therefore, the Secretary has concluded that the only appropriate standard by which to assess a cost-sharing demonstration project, including its potential effect on Medicaid beneficiaries, is the standard established by section 1115 itself—whether the project is "likely to assist in promoting the objectives" of the Medicaid program. On the basis of that standard, and pursuant to the waiver authority contained in 45 CFR 46.101(e), the Secretary believes that a waiver is appropriate since IRB review would constitute an inappropriate and unnecessary step in the evaluation and approval of section 1115 Medicaid cost-sharing demonstration projects.

Since there are important reasons for expediting the conduct of research on the use of Medicaid cost-sharing, and it is this Department's policy generally to eliminate unnecessary procedures in the administration of its programs, the waiver announced in this notice is effective immediately (March 4, 1982).

Dated: February 25, 1982.

Richard S. Schweiker,

Secretary.

[FR Doc. 82-5723 Filed 3-3-82; 8:45 am]

BILLING CODE 4120-03-M

Federal Register / Vol. 47, No. 55
Monday, March 22, 1982

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

45 CFR Part 46

Exemption of Certain Research and Demonstration Projects From Regulations for Protection of Human Research Subjects

AGENCY: Department of Health and Human Services.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Department of Health and Human Services (the Department or HHS) is proposing to include among the types of research specifically exempt from the application of the regulatory requirements of 45 CFR Part 46 (protection of human research subjects), research and demonstration projects conducted under the Social Security Act and other Federal statutory authority and designed to study certain public benefit or service programs, the procedures for obtaining benefits or services under those programs, and possible changes or alternatives to those programs or procedures, including changes in methods or levels of payment. This proposed amendment to the revised final regulations for protection of human research subjects (published January 26, 1981) would, in effect, restore to the regulations an exemption included in the initial notice of proposed rulemaking (NPRM) (published August 14, 1979). These demonstration and service projects are already subject to procedures which provide for extensive review by high level officials in various program administration offices. Review by an IRB would be duplicative and burdensome to state and local agencies and to other entities participating in demonstration projects. Removal of an unnecessary layer of review will not only reduce the cost of the projects but help to avoid unnecessary delays in project implementation.

DATE: Written comments are due by April 21, 1982.

ADDRESS: Please send comments or requests for additional information to: F. William Dommel, Jr., J. D., Assistant Director, Office for Protection from Research Risks, Public Health Service, 5333 Westbard Avenue, Room 3A–18, Bethesda, Maryland 20205. Telephone: (301) 496–7163.

FOR FURTHER INFORMATION CONTACT: F. William Dommel, Jr.; (301) 496–7163.

SUPPLEMENTARY INFORMATION: In an NPRM published August 14, 1979 (44 FR 47688), the Department proposed amendments to the basic HHS Policy for the Protection of Human Research Subjects, 45 CFR Part 46, and included an exemption from these regulations for research "designed to study on a large scale: (A) The effects of proposed social or economic change, or (B) methods or sytems for the delivery of or payment for social or health services." Public comment on this section of the NPRM focused on the lack of clarity of its wording, and in particular the vagueness of the phrase "on a large scale." (See discussion in the preamble to the final amended regulations. 46 FR 8366, 8370, January 26, 1981.) No significant questions were raised and few adverse comments were made about exempting from institutional review board (IRB) scrutiny, research which involves the study of existing public benefit or service programs and possible changes in or alternatives to those programs. However, at the time of publication of the final regulations, the Department did not elect to include this exemption, but instead, as a policy matter, found IRB review "appropriate" for such research, while permitting waiver of informed consent where it is found to be "impracticable" (46 FR 8383).

The principal authority for the regulations in Part 46 is found in section 474 of the Public Health Service (PHS) Act under which the Secretary is required to establish by regulation review procedures for "the conduct of biomedical and behavioral research involving human subjects." This legislation does not specifically address research and demonstration projects designed to study public benefit or service programs which are conducted under the Social Security Act and other statutory authority. The Department again proposes to exempt certain projects of this kind as it previously proposed to do in the NPRM published August 14, 1979 (44 FR 47688). The specific wording of the exemption, however, has been modified in response to public comments which the Department received concerning the language proposed earlier. These comments call for greater clarity and specificity in the wording of the exemption.

There are several reasons why the Department considers such an exemption to be appropriate. First, these demonstration and service projects are already subject to procedures which provide for extensive review by high level officials in various program administration offices. Review by the IRB would be duplicative and burdensome to state and local agencies and to other entities participating in demonstration projects. Removal of an unnecessary layer of review will not only reduce the cost of the projects but help to avoid unnecessary delays in project implementation.

Second, it is reasonable to assume that when the Congress directed that public benefit and service programs be carried out, it also expected the funding agencies to be able to evaluate them without subjecting the evaluation efforts to review and possible disapproval by IRBs.

Finally, the Department believes that the review procedures set forth in the current regulations are not well suited for demonstration projects involving public benefit and service programs. The Department has already provided for waiver of some or all of the consent procedures which are appropriately required for other kinds of research, but which may not be practicable for demonstration projects. The exemption proposed herein in simply a logical extension.

Under the proposed exemption, research and demonstration projects with the following statutory authorities would be among those exempted from the Part 46 requirements: Sections 426, 445, 1110(a), 1115 and 1875 of the Social Security Act; sections 201 (a) and (b) and section 505 of the Social Security

Disability Amendments of 1980, Pub. L. 96–265; Section 402(a) of the Social Security Amendments of 1967, as amended (codified at 42 U.S.C. 1395b–1); section 222(a) of the Social Security Amendments of 1972 (codified at 42 U.S.C. 1395b–1 note); section 649 of Pub. L. 97–35 (Head Start Act); section 4 of Pub. L. 93–247, as amended (Child Abuse Prevention and Treatment Act); section 145 of Pub. L. 91–517, as amended (Developmental Disabilities Assistance and Bill of Rights Act); section 805 of Pub. L. 93–644, as amended (Native American Program Act of 1974); sections 421–425 of Pub. L. 93–29, as amended (Older Americans Act of 1965).

Impact Analysis

Economic Impact on Small Entities

The Secretary certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities within the meaning of the Regulatory Flexibility Act, Pub. L. 96–354. Thus, a regulatory flexibility analysis is not required.

Classification of Rule Under E.O. 12291

The Secretary has determined that this rule is not a "major rule" under Executive Order 12291 and thus a regulatory impact analysis is not required. The Secretary's determination is based on the finding that the proposed rule would not:

(1) Have an annual effect on the economy of $100 million or more;

(2) Impose a major increase in costs or prices for consumers, individual industries, Federal, State or local government agencies, or geographic regions; or

(3) Result in significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

Notice is given that it is proposed to make any amendment that is adopted, effective upon publication in the **Federal Register.**

Dated: February 1, 1982.

Edward N. Brandt, Jr.,
Assistant Secretary for Health.

Approved: February 25, 1982.

Richard S. Schweiker,
Secretary.

PART 46—PROTECTION OF HUMAN SUBJECTS

For the reasons set out in the preamble, Part 46 of 45 CFR is proposed to be amended by adding a new paragraph (6) to § 46.101(b) to read as follows:

§ 46.101 [Amended]

* * * * *

(b) * * *

(6) Unless specifically required by statute, research and demonstration projects which are conducted by or subject to the approval of the Department of Health and Human Services, and which are designed to study, evaluate, or otherwise examine: (i) Programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

* * * * *

§ 46.116 [Amended]

Additionally § 46.116(c) is to be removed and § 46.116 (d), (e) and (f) are to be redesignated as § 46.116 (c), (d) and (e) respectively.

[FR Doc. 82–7565 Filed 3–19–82; 8:45 am]

BILLING CODE 4160–17–M

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

March 12, 1982

The Honorable Richard S. Schweiker
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Schweiker:

Thank you for your letter of March 9 expressing your Department's endorsement of the medical aspects of the Commission's conclusions on the determination of death and your deference to the Department of Justice on the statutory aspects. Furthermore, the Commission is pleased to note the progress being made collaboratively between your staff and ours in resolving matters of common concern regarding the interpretation of the HHS regulations on human subjects.

I write now on behalf of the Commission for clarification of your Department's interpretation regarding the applicability to social policy experiments of the regulations governing research with human subjects (45 CFR 46). The question is whether research designed, for example, to test the effect of requiring co-payment for services under Medicaid falls within the ambit of the regulations. Last year, Dr. Charles McCarthy, the HHS liaison to the Commission, in interpreting the regulations for us stated the Department's view that IRB review of research would be "particularly appropriate" when the waiver provisions of §46.116(c) are invoked to relieve researchers of the requirement of obtaining informed consent in large-scale social policy experiments. (The full statement appears in the enclosed correspondence.)

As Dr. McCarthy explained, the August 1979 draft of the HHS regulations exempted certain large-scale social policy experiments. "After extended debate," in Dr. McCarthy's words, "the Department decided not to include that exemption in the final regulations." Yet in a notice of waiver published in the March 4, 1982, Federal Register (47 Fed. Reg. 9208), you have waived all application of 45 CFR 46 to research on Medicaid designed to test variations in co-payments, deductibles and co-insurance.

I recall that at our meeting last December you emphasized the importance of the Department's speaking to the Commission with one voice, through Dr. McCarthy, on matters relating to research with human subjects. Yet his interpretation of the intent of those regulations seems to have been overturned without benefit of the "extended debate" and prolonged rulemaking process which led to the development of the revised regulations issued in January 1981.

The Commission would appreciate learning more about the policy considerations that underlie the recent decision to waive IRB review of research on Medicaid. In particular, we are concerned about two points:

1. It appears that your decision to waive 45 CFR 46 would be equally applicable to all large-scale social policy experiments conducted or sponsored by the Department. Does this not, in effect, create an exemption for such research?

2. Since the district court in Crane v. Mathews, in upholding a challenge to an earlier Medicaid experiment that had been commenced without following the Department's regulations on human subjects' protection, found that potential medical risks were created by co-payment research, would it not be, as the OPRR concluded, "particularly appropriate" to have IRB review when consent will not be sought?

The Commission thanks you for your attention to these questions and looks forward to your response.

Sincerely yours,

Morris B. Abram
Chairman

Enclosures: Letters of January 28, 1981
and February 26, 1981
47 Fed. Reg. 9208

cc: Dr. Robert Rubin, ASPE
Dr. Charles McCarthy, OPRR

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
2000 K Street, N.W., Suite 555, Washington, DC 20006 (202) 653-8051

January 28, 1981

Charles R. McCarthy, Ph.D.
Director
Office for Protection from Research Risks
National Institutes of Health
5333 Westbard Avenue, Room 3A-18
Bethesda, Maryland 20205

Dear Charlie:

Now that we have had a few days to review the new regulations (45 CFR 46) I would like to express my personal pleasure at the extent to which the Department has managed to interpret and implement so fully the recommendations of the National Commission as well as the suggestions proposed by the President's Commission. In addition, I am tremendously impressed ... the amount of effort that clearly must have been involved in bringing the task to fruition.

In reading through the various sections, however, one question has arisen which we would be grateful if you could clarify for the record. We recognize that the definition of research explicitly includes research activities that may be part of service programs (§46.102(e)) and that the Department expressly decided (46 Federal Register 8366, 8370, January 26, 1981) not to exempt from IRB review "research designed to study on a large scale... methods or systems for the delivery of or payment for social or health services," as had originally been proposed in August 1979. A question remains as to the current status of the "interpretation" issued by Secretary Mathews on June 28, 1976 (41 Federal Register 26572) regarding the meaning of "subject at risk," particularly for research of the type involved in Crane v. Mathews. Since it was not explicitly rescinded in the preamble to the revised regulations, we would appreciate knowing the Department's current understanding of the status of that "interpretation".

I am sending a copy of this letter to Dick Riseberg as I assume you and he will be working together on a response.

Sincerely yours,

Barbara

Barbara Mishkin
Deputy Director

cc: Mr. Richard Riseberg

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

February 26, 1981

Ms. Barbara Mishkin, Deputy Director
President's Commission for the Study
of Ethical Problems in Medicine and
Biomedical and Behavioral Research
2000 K Street, NW - Suite 555
Washington, D.C. 20006

Dear Barbara:

Thank you for your recent letter expressing satisfaction with the Department of Health and Human Services (HHS) regulations for the protection of human subjects involved in research. As a contributor to the effort, you are well aware of the years of careful planning which went into their development. Now that the task is complete, we have hardly had time to catch our breath before going on to the equally challenging task of assisting HHS-funded institutions as they endeavor to understand and then implement the new provisions. Our burden is somewhat eased by the fact that the new policy represents significant deregulation, while continuing to afford necessary protections for the rights and welfare of human subjects.

Your letter requested, for the record, a clarification of the "status of the 'interpretation' issued by Secretary Mathews on June 28, 1976, regarding the meaning of 'subject at risk', particularly for research of the type involved in *Crane v. Mathews*." It is our position that the Mathews interpretation, which was addressed to the regulations then in effect, does not apply to the new regulations. You will recall that the proposed regulations of August 14, 1979 (44 FR 47688) contained an exemption for certain large-scale program research. After extended debate, however, the Department decided not to include that exemption in the final regulations. Instead the new regulations provide for Institutional Review Board (IRB) waiver of the informed consent requirements where:

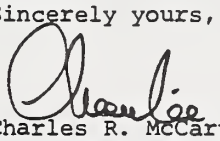
> *(1) The research is to be conducted for the purpose of demonstrating or evaluating: (i) federal, state or local benefit programs which are not themselves research programs, (ii) procedures for obtaining benefits or services under these programs, or (iii) possible changes in or alternatives to these programs or procedures; and (2) the research could not practicably be carried out without the waiver ... .*

We believe that IRB review of such evaluation research involving human subjects is appropriate even where, and perhaps particularly where, informed consent is not required.

Page 2 - Ms. Barbara Mishkin

Bill Dommel and I have discussed this interpretation with Dick Riseberg and he concurs with this opinion.

Sincerely yours,



Charles R. McCarthy, Ph.D.
Director, Office for Protection
from Research Risks
Office of the Director

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

April 21, 1982

Mr. F. William Dommel, Jr.
Assistant Director
Office for Protection from
Research Risks
Public Health Service
Room 3A-18
5333 Westbard Avenue
Bethesda, Maryland 20205

Dear Mr. Dommel:

Attached are the comments of the President's Commission on the proposal published on March 22, 1982, by the Department at 47 Federal Register 12276. The Commission trusts that the Department will take account of these comments in evaluating the proposed amendment to 45 CFR 46 and respond to them, pursuant to the provisions of Sec. 1802(b) of the Public Health Service Act, 42 U.S.C. Ch. 6A, Subch. XVI, §300v-1(b).

Sincerely,

Morris B. Abram
Chairman

Enclosure

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

April 21, 1982

Comments of the President's Commission
on the Department of Health and Human Services'
March 22, 1982 Notice of Proposal to
Exempt Certain Research Projects from 45 CFR 46

The President's Commission agrees with the Department of Health and Human Services (HHS) that properly conducted research on governmental benefit programs can provide valuable information and should be encouraged. It is important that public policy rest on a firm base of knowledge about its costs and benefits. It is equally important that such knowledge be obtained in a way that respects the rights and well-being of all involved.

The Commission has been given specific responsibility by the Congress to examine the adequacy and uniformity of the Federal regulations governing biomedical and behavioral research with human subjects. In its first Biennial Report on this subject, transmitted to the Department in December 1981, the Commission described the Department's regulations (45 CFR 46) as the model for a consolidated government-wide system. The Commission recognized that those regulations were issued in January 1981 only after a long and conscientious review of the views of the National Commission for the Protection of Human Subjects and of many other parties.

In light of this background of the HHS regulations, the Commission found itself with several questions as a result of the Department's March 4, 1982 notice in the Federal Register, waiving the application of 45 CFR 46 to research on Medicaid designed to test variations in co-payments, deductibles and co-insurance. On March 12, 1982, the Commission wrote to Secretary Schweiker concerning that notice of exemption. Several of the issues raised in that letter are germane to the March 22, 1982 notice proposing an across-the-board exemption for large categories of social policy experiments under the Department's jurisdiction. In addition, the Commission has the following concerns about the March 22 proposal:

1. Duplicative Review

The Commission shares the Department's desire to avoid review that is "duplicative." If present processes provide the same protections for research subjects that is intended by 45 CFR 46 in requiring prior review and approval by a properly constituted Institutional Review Board (IRB) for all research involving human subjects supported by HHS funds, then the goals of 45 CFR 46 would be met and the formal requirement of IRB approval would appear duplicative.

In order to support the conclusion of "duplication," the review process employed within HHS in lieu of the IRB process would have to provide, at a minimum: (1) review by persons unassociated with the program management and with no interest in the outcome of the research; (2) the inclusion among the reviewers of non-government personnel; and (3) reviewers with qualifications as well as responsibility for evaluating the ethical aspects of the research in addition to technical, fiscal, and programmatic soundness.

Since the March 22 notice does not set forth the nature of the review process that has been or will be used in lieu of IRB review, it is not possible to evaluate the assertion that requiring IRB review would be "duplicative."

2. Informed Consent

Requiring "informed consent" from all affected persons would defeat many social policy experiments of the type covered by the March 22 proposal. This difficulty is recognized by 45 CFR §46.116(c) which permits an IRB to waive the informed consent requirements for projects to evaluate benefit and service programs and possible alterations in such programs. The Commission regards this as a necessary and proper power for IRBs.

Two points bear emphasis, however. First, under the regulations, it is an IRB--and not the sponsors of the research or other officials of the Department--which is given this authoirty by the HHS regulations. Second, as the Office for Protection from Research Risks informed the Commission on February 26, 1981, it is "particularly appropriate" for all aspects of a research project to undergo IRB review when the consent waiver provision is employed. Since subjects will not have the opportunity to give or withhold their informed consent to participation in the research, it is desirable that their interests and risks be reviewed by an independent body

3. Risks

HHS dismisses the notion that any risks exist for subjects in social policy experiments in the categories encompassed within the proposed exemption to 45 CFR 46. The Commission finds that several types of possible harm exist; this raises serious questions about the basis for the Department's proposed exemption.

A. The Department does not address the question of the medical risks generated by such experiments. In Crane v. Mathews, the district court found that copayment experiments present medical risk to recipients of health care services normally available without such copayment because participants might be unable (or perceive themselves to be unable) to afford the copayment and might thus go without necessary medical care.

B. Even when no physical (medical) risks are imposed, certain aspects of evaluation research involve issues of nonphysical risk with which IRBs are familiar, such as (1) surveys and questionnaires involving personal matters that are usually confidential or that would expose respondents to legal penalties or other detriment if known, (2) review of personally identifiable health records by persons not ordinarily authorized to see such records, and so forth.

In light of these factors, the Commission believes that substantial justification is needed to eliminate the protections provided for subjects' interests by prior IRB review of research projects.

4. Statutory Basis

The Department fails to distinguish program alterations which it has statutory authority to make in the Secretary's discretion, from changes which (like the copayment requirement in Medicaid), are in fact prohibited by the agency's enabling legislation. What is proposed in the latter case is not an evaluation of an ongoing program, fully authorized by Congress, but rather, the imposition of burdens on some persons that the Congress has generally forbidden be imposed on beneficiaries of the program in question. The justification for such burdens is the knowledge to be gained from conducting the experiment (knowledge which the Commission agrees may be very important to have). Again, the need for a balancing of these two factors suggests to the Commission the value in the dispassionate evaluation provided by an IRB.

5. Benefits v. Detriments

A related issue about the type of experiment--also not mentioned by HHS--arises independently of the statutory issue. Although concerns over equality arise whenever people who are similarly situated are treated differently by the government, other groups that have examined the issue have seen a difference between experiments involving provision of a benefit not otherwise available or to which the subjects are not otherwise entitled and one involving the withholding or reduction of benefits or services to which the subjects are legally entitled.

A. The National Commission for the Protection of Human Subjects recommeded "expedited review" for program evaluation research only if the projects "entail no deviation for subjects from the normal requirements of their involvement in the program being evaluated or benefits related to their participation in such program" (Recommendation 5, comment H, p. 35 of the National Commission's Report and Recommendations on Institutional Review Boards).

B. In not adopting the rules proposed in August 1979, HHS rejected proposed exemption of social policy research and adopted instead the National Commission's recommendation that such research receive expedited review.

The Department thus overstates when it says that the proposed rules would "reintroduce" provisions previously proposed. Rather, the proposed rules would introduce, for the first time, exemptions which both the National Commission and the Department itself previously rejected on principle. The March 22 notice does not contain any argument to justify the conclusion that "expedited review" would not adequately protect researchers in appropriate cases or that full IRB review should not occur in cases where deviation occurs in the provision of normal program benefits.

CONCLUSION

In sum, the Commission concludes that the broad exemption proposed by the Department should be drawn more narrowly to take into account the concerns expressed above. The attention of the Department is again drawn to the proposal, which was part of a submission made to Secretary Patricia Harris on September 18, 1980 (see pp. 166-173 of the Biennial Report), for a systematic treatment of the exemptions now found in Section 46.101(b). In particular, the Commission recognized the special justification for social policy experiments, some of which were seen to need IRB review while others, described as follows, would not:

> These regulations do not apply to research designed to evaluate federally sponsored social, economic, or health service programs, or proposed changes in such programs, where: (1) the appropriate Departmental official has been given explicit Congressional authority to modify a program for research purposes, (2) the programs or changes to be evaluated are themselves within the statutory authority of the agency to adopt, and (3) the research involves no limitation or withholding of a benefit to which the subjects are legally entitled or which other individuals, similarly situated, continue to receive under the program being evaluated.

The Commission urges the Department to reconsider the proposed exemption and would be pleased to work with the Department's representatives to fashion a mechanism that will be appropriately expeditious and nonduplicative of any procedures already employed by the Department. The Commission's objective, which it hopes is shared by the Department, is to see that human subjects in experiments conducted by HHS are provided the same protection as the Department's rules require other research institutions to assure in their government-funded research.

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUN 23 1982

Mr. Morris B. Abram, Chairman
President's Commission for the Study
of Ethical Problems in Medicine and
Biomedical and Behaviorial Research
2000 K Street, NW - Suite 555
Washington, D.C. 20006

Dear Mr. Abram:

This responds to your letter in which you raise certain questions concerning applicability of the Department's Regulations for the Protection of Human Subjects (45 CFR 46) to projects conducted under the Department's demonstration authority which involve modification of medical assistance or other forms of social welfare benefits. More specifically, you seek clarification of the relationship between the regulations and proposed demonstration projects requiring cost-sharing (in the form of co-payments, deductibles or coinsurance) of Medicaid recipients.

As your letter indicates, the applicability of the regulations to such demonstration projects has been the subject of "extended debate" within the Department. Originally, these projects were intended to be excluded from the scope of the regulations (44 Fed. Reg. 47688). When the final regulations were published, however, they covered such projects. Recently, after further consideration the Department proposed once again to remove these projects from the regulations' coverage (47 Fed. Reg. 12276). As described more fully in the Federal Register Notice, this proposal was essentially based on the realization that the extensive protections provided by the regulations to human subjects were inappropriate and unnecessary in the context of social welfare demonstrations.

In the meantime, the Department also became aware of particular problems with application of the regulations to one type of demonstration project, involving imposition of co-payments and other cost-sharing requirements. Accordingly, we decided to waive the application of the regulations to this particular class of demonstration projects. Such waiver was of course contemplated by the regulations and specifically provided for in 45 CFR 46.101(e). The reasons underlying the decision to grant such a waiver are set forth in the Federal Register Notice announcing it (47 Fed. Reg. 9208).

Page 2 - Mr. Morris B. Abram

I am informed by the General Counsel's Office that the granting of a waiver in such circumstances is consistent not only with the regulations but also with the court's decision in Crane v. Mathews, 417 F. Supp. 532 (N.D. Ga. 1976). The court in Crane specifically declined to consider whether co-payments placed individuals at risk. See 417 F. Supp. at 546. Instead, it simply held that persons required to participate in a co-payments demonstration project were "human subjects" within the meaning of the regulations and thus intended to be covered thereby. This finding in no way precludes a decision by the Department to waive IRB review in the manner expressly provided in the regulations.

I appreciate your concern on this issue and will see that your comments are considered in connection with the pending proposal to eliminate IRB review entirely for demonstration projects under §1115 and other similar authorities.

Sincerely,

Richard S. Schweiker
Secretary

HHS Final Rule on Exemption of Social Policy Experiments from 45 CFR 46

Federal Register / Vol. 48, No. 44 / Friday, March 4, 1983

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

45 CFR Part 46

Exemption of Certain Research and Demonstration Projects From Regulations for Protection of Human Research Subjects

AGENCY: Office of the Secretary, Department of Health and Human Services.

ACTION: Final rule.

SUMMARY: The Department of Health and Human Services (the Department or HHS) is including among the types of research specifically exempt from the application of the regulatory requirements of 45 CFR Part 46 (protection of human research subjects) research and demonstration projects conducted under the Social Security Act and other federal statutory authority and designed to study certain public benefit or service programs, the procedures for obtaining benefits or services under those programs, and possible changes or alternatives to those programs or procedures, including changes in methods or levels of payment. These demonstration and service projects are already subject to procedures which provide for extensive review by high level officials in various program administration offices. Review by an Institutional Review Board (IRB), as required under Part 46, would be duplicative and burdensome to state and local agencies and to other entities participating in demonstration projects. Removal of this unnecessary layer of review will not only reduce the cost of the projects but help to avoid unnecessary delays in project implementation. However, in order to ensure the continued protection of human subjects participating in such research activity, the Department is adding a specific requirement of written, informed consent in any instance, not reviewed by an IRB, in which the Secretary determines that the research activity presents a danger to the physical, mental or emotional well-being of a participant.

EFFECTIVE DATE: These regulations are effective April 4, 1983.

FOR FURTHER INFORMATION CONTACT: F. William Dommel, Jr.; (301) 496–7163.

SUPPLEMENTARY INFORMATION: In a notice of proposed rulemaking (NPRM), published March 22, 1982, 47 FR 12276, the Department proposed to exempt certain research and demonstration projects from coverage of the

Regulations for the Protection of Human Subjects, 45 CFR Part 46. The research activity proposed for exemption from the regulations generally involves public benefit or service programs under the Social Security Act and other similar programs administered by the Department. Such projects typically study proposed or possible changes in levels of benefits or services or in the systems and procedures for delivering such benefits or services to recipients. As indicated in the NPRM, the Department now believes that such research activity is fundamentally different from the experiments and projects otherwise covered by the Part 46 regulations, which typically involve biomedical or behavioral research.

The NPRM noted that the Department had previously proposed to exempt this class of research activity from the Part 46 regulations. 44 FR 47688 (August 14, 1979). However, when the regulations were published in final form, they continued to cover these activities. 46 FR 8366, 8370 (January 26, 1981). As a result, research and demonstration projects carried out under the Social Security Act and other statutes for the purpose of studying possible changes in benefit levels or in procedures for delivery of benefits have been subject to a requirement of review by an Institutional Review Board (IRB). The Department's experience has been that this additional layer of review for such projects is duplicative and needlessly burdensome in light of the substantial review process to which they are already subjected by state and federal officials. Furthermore, the Department has found such review by an IRB—which generally focuses on ethical questions arising from biomedical and behavioral research—to be unnecessary and inappropriate in the context of adjustments to benefit and service programs.

In view of these considerations, the Department proposed to exempt this class of research activity from the Part 46 regulations. In doing so, we indicated the following statutory authorities for conducting such research activity as among those which would be exempt from the regulations if the proposed exemption were adopted: Sections 426, 445, 1110(a), 1115 and 1875 of the Social Security Act; section 201 (a) and (b) and section 505 of the Social Security Disability Amendments of 1980, Pub. L. 96–265; section 402(a) of the Social Security Amendments of 1967, as amended (codified at 42 U.S.C. 1395b–1); section 222(a) of the Social Security Amendments of 1972 (codified at 42 U.S.C. 1395b–1 note); section 649 of Pub. L. 97–35 (Head Start Act); section 4 of Pub. L. 93–247, as amended (Child Abuse Prevention and Treatment Act); section 145 of Pub. L. 94–103, as amended (Developmental Disabilities Assistance and Bill of Rights Act); section 805 of Pub. L. 93–644, as amended (Native American Program Act of 1974); sections 421–425 of Pub. L. 93–29, as amended (Older Americans Act of 1965). Section 702 of the Social Security Act is another example of a statutory authority for conducting research which would be exempt from the Part 46 regulations under the exemption we proposed.

We have now carefully considered the comments received in response to the NPRM. These comments are analyzed and addressed below. As indicated, nothing in the comments led us to conclude that this class of research activity should, as a matter of policy, be subject to IRB review as provided by the Part 46 regulations. Moreover, in contrast to biomedical and behavioral research sponsored or conducted by the Department under the Public Health Service Act, there is no statutory requirement that such research activities be reviewed by an IRB.

Nevertheless, the Department does have an obligation, pursuant to the conditions imposed upon its continuing appropriations, to ensure that research activity not present a danger to the physical, mental or emotional well-being of participants. See, e.g., section 412, Pub. L. 93–517. In order to make clear that we will continue to fulfill that obligation and also in response to certain of the comments received, we are adding language to Part 46 to clarify that, with respect to research activity involving public benefit programs now to be exempted from IRB review, the Department will include in its review of such proposed research activity

consideration of the effects on participants. To the extent that the proposed activity is determined to pose a danger to the participants, informed consent in writing will be required. This clarification will apply only to those projects which were previously subject to IRB review but are now exempt. All other categories of exempt research set forth in § 46.101(b) will continue not to be subject to any requirement of review for purposes of protecting human subjects since these other categories involve little or no possibility of risk to participants. See 46 FR 8367 (January 26, 1981).

In addition, our review of the proposal and the comments has led us to adopt another refinement to the final regulation. In the NPRM, we indicated that we were deleting entirely the provision in § 46.116(c) which permitted waiver of informed consent by IRB's in certain situations involving Federal, state or local benefit or service programs. The proposed deletion of this provision was prompted by the recognition that this waiver authority would not be needed in circumstances covered by the new exemption—*i.e.*, research or demonstration projects involving public benefit or service programs "conducted by or subject to the approval of" this Department. However, the new exemption does not reach similar projects conducted by or subject to the approval of state or local governments. There was no intention to impose additional burdens on such research carried out under the auspices of state or local government. Accordingly, we have determined that it would be appropriate to continue providing the authority under § 46.116(c) for an IRB to waive informed consent in circumstances where a research or demonstration project involves public benefit or service programs and where the project is conducted by or subject to the approval of state or local governments. The language of the new § 46.116(c) has beem amended slightly to conform to the language of the new exemption.

Response to Comments

We received approximately 50 comments in response to the proposed exemption. Most of these comments came from advocacy groups who regularly represent, in court and otherwise, persons whose benefits might be affected by the research projects proposed to be exempted from the Part 46 regulations, and most of them opposed the exemption for one reason or another. Favorable comments were received from several States which generally agreed with the analysis in the NPRM that IRB review of such projects was burdensome and duplicative. Below we have summarized, discussed and responded to the major comments, organized by topic, which were submitted in opposition to the proposed exemption.

1. Some commenters objected to the fact that we did not publish in the notice of proposed rulemaking an exhaustive list of every statutory demonstration authority to which the exemption would pertain. According to these commenters, fairness required a complete listing of every statute pursuant to which a demonstration project might be conducted exempt from the regulations. This suggested approach ignores the fact that the regulations themselves are couched in terms of broad categories of research. In listing the statutory authorities subject to the proposed exemption, we provided prominent examples of the types of authority which would be exempt. In view of the large number of statutory authorities, which are frequently augmented by legislation, we believe that an effort to provide an exhaustive list could be misleading since such a list would inevitably be incomplete. Thus, we did not attempt to catalogue all exempt authorities since the clear intent of the proposed exemption is to cover all projects failing within its terms, whether or not they were specifically referenced in the notice of proposed rulemaking.

2. A few commenters asserted that the list of statutory authorities subject to the proposed exemption was in fact inaccurate because section 505 of the Social Security Disability Amendments of 1980, Pub. L. 96–265, requires that projects conducted thereunder be subject to the Department's regulations for the protection of human subjects. Such comments appear to be based on a

misunderstanding as to the scope of the demonstration authority enacted by section 505. That statute created a new demonstration authority relating to the work activity of disabled beneficiaries under the old-age, survivors and disability insurance program. This new authority is not required to be covered by the Department's regulations governing informed consent and the protection of human subjects. However, section 505 also amended section 1110 of the Social Security Act to add a new subsection (b) providing authority to waive requirements of Title XVI (the Supplemental Security Income program) for the purposes of carrying out demonstration projects. The statute expressly provides that projects conducted pursuant to this authority are subject to "the requirements for informed consent established by the Secretary for use in any experimental, pilot, or demonstration project in which human subjects are at risk." Thus, we recognize that demonstration projects carried out under section 1110(b) are required to be covered by the Part 46 regulations, and for that reason they were not included among the authorities to which the proposed exemption would apply.

3. A number of the comments referred to the decision of the court in *Crane* v. *Mathews,* 417 F. Supp. 532 (N.D. Ga. 1976), as contrary to the proposed exemption. In that case, Georgia Medicaid recipients challenged a demonstration project permitting the state to impose copayments for medical services pursuant to a waiver of statutory provisions otherwise barring such copayments. The plaintiffs alleged, among other things, that the Department's then effective regulations for protection of human subjects required that such projects be first reviewed by an IRB. The court agreed and enjoined the project pending IRB review in accordance with the regulations.

In fact, contrary to the suggestion of these comments, the *Crane* court did not hold that demonstration projects under the Social Security Act were required to be subject to the Part 46 regulations. Instead, the court simply found that the regulations as then in effect were intended to cover such demonstration projects, at least as they pertained to imposition of copayments upon Medicaid recipients. Furthermore, the court in no way concluded that the recipients were placed at risk by the demonstration project. Nothing in the *Crane* decision can be read as mandating the retention of Part 46 coverage in the case of the demonstration projects which we are now exempting from the regulations.

4. Several comments took issue with the manner in which the notice of proposed rulemaking discussed our statutory authority to regulate experiments other than biomedical and behavioral research. We noted that the principal authority for the Part 46 regulations was section 474 of the Public Health Service Act, which requires the Secretary to establish regulations governing "the conduct of biomedical and behavioral research involving human subjects" and specifies that an IRB shall be the vehicle for review of such research. In so noting, we in no way meant to imply that we lacked statutory authority to regulate the sorts of experiments and demonstration projects which we now are exempting from IRB review under the Part 46 regulations. As the court held in *Crane* v. *Mathews,* it is clearly within the broad rulemaking authority of the Secretary to regulate activity of that nature. However, in exempting it from IRB review, we felt it appropriate to distinguish this activity from biomedical and behavioral research, where we are mandated by statute to impose such review.

Other comments suggested that certain demonstration projects under the Social Security Act which we are now exempting from IRB review in fact feature considerable biomedical or behavioral aspects, thus bringing them within the scope of section 474's mandate. While the phrase "biomedical and behavioral research" is susceptible to broad interpretation, we see no indication that Congress intended the requirements of section 474 to apply to the demonstration projects subject to the proposed exemption. When passing legislation providing waiver or demonstration authority under the

Social Security Act, Congress has made explicit those circumstances in which it believes that human subjects should be protected by an additional layer of regulatory review. See, for example, section 1110(b) of the Social Security Act. Thus, we believe that it is totally consistent with the intent of Congress in passing section 474 that we exempt from IRB review projects involving social welfare and benefit programs. The court in *Crane* v. *Mathews* agreed with our view that section 474 does not require regulation of such projects. See 417 F. Supp. at 545.

5. Some comments objected that the proposed exemption did not give sufficient consideration to the recommendations of the various National and Presidential Commissions that have studied the issue of protection of human subjects. We believe that we have addressed the major concerns of those Commissions and their findings. The Commissions have focused principally on problems stemming from biomedical and behavioral research involving human subjects. Nevertheless, we have experimented with broader use of IRB review. As we indicated in the notice of proposed rulemaking, our experience with IRB review led us to conclude that it was in fact unnecessary and burdensome in the context of research concerning benefit programs under the Social Security Act and otherwise. Throughout this process, we have continued to consider, evaluate and place great weight upon the comments of these Commissions. In fact, as discussed below, dialogue with the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has also continued with respect to the proposed exemption.

6. Among the commenters was the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The Commission noted that review by state and federal officials did not precisely "duplicate" IRB review unless the reviewers included persons independent of program management, including non-government personnel and persons with expertise in "ethical" aspects of research. Recognizing that "informed consent" requirements could easily frustrate social policy experiments of the sort proposed for exemption, the Commission nevertheless suggested that this concern could be addressed by the waiver provisions in the regulations. In the Commission's view, however, such waivers should be issued by an IRB rather than by the decision of either state or federal program officials. The Commission also suggested that research projects covered by the proposed exemption can create medical risks as well as risks of non-physical intrusions into personal or confidential matters and that such risks should be considered by an IRB. The Commission expressed particular concern about research entailing reduction of benefits to certain recipients while others, similarly situated, continue to receive a higher level of benefits. In light of this concern, the Commission proposed an alternative exemption which would not include such research. Thus, under the Commission's alternative, research projects in any way limiting or reducing the benefits to which recipients would otherwise be entitled would continue to be subject to IRB review.

We have considered the Commission's comments with particular care in recognition of its statutory mandate in the area of ethical problems in research. We have decided, however, not to follow the Commission's suggestion that the exemption be limited to those research projects not entailing reduction of benefits. A review of the research projects covered by the proposed exemption reflects that many, if not most, of them could be construed as reducing benefits in one way or another. Accordingly, adoption of the Commission's alternative would not adequately address the concerns which prompted us to propose the exemption.

We do not agree with the Commission's belief that the "ethical" aspects of research in benefits programs will go unreviewed unless nongovernmental individuals with expertise in the ethics of research participate in consideration of proposed studies. The questions raised by research involving government benefits

are significantly different from those raised by biomedical and behavioral research. IRB's are typically constituted to deal with the special ethical and other problems involved in biomedical and behavioral research. In contrast, ethical and other problems raised by research in benefit programs will be addressed by the officials who are familiar with the programs and responsible for their successful operation under state and federal laws. The risks identified by the Commission can be sufficiently evaluated by those program officials.

7. Some comments disagreed with the NPRM's conclusion that IRB review was duplicative and unnecessary in the context of the research projects proposed for exemption. These comments focused on the need for an independent reviewing body to ensure that recipient rights were properly considered and expressed doubt as to the ability of state officials in particular to fulfill that role. In our view, these comments ignore the fundamental difference between such research projects and biomedical and behavioral research. In contrast to the latter, which may result in either significant physical invasions or intrusions upon the privacy of participants, research in public benefit programs typically involves alterations in eligibility criteria, benefit levels or delivery systems. These are matters not falling within the expertise of IRB members but instead within the knowledge and experience of program officials at both the state and federal levels. In the course of promulgating regulations for the various programs at issue, these officials are regularly called upon to make decisions of the same sort, entailing determinations as to which persons may or may not receive benefits and at what levels. In that sense, the research projects proposed for exemption do not differ substantially from the normal program activity administered by these officials. Furthermore, with the addition of clarifying language to the Part 46 regulations, there will be a well-defined responsibility of federal program officials to take into consideration potential risks to the health and safety of participants in research activity before making decisions whether or not to approve particular projects.

With respect to the adequacy of review by state program officials, we have no basis to question either the competency or sincerity of state personnel. In any event, research proposals by the states receive thorough review by federal officials experienced in the various programs. It is significant to note that the major Medicaid research authority—section 1115 of the Social Security Act—specifically provides that projects thereunder be consistent with the purposes of the program. In reviewing state proposals, federal officials will be mindful, as always, of this injunction.

8. Certain comments suggested that, in proposing to exempt from IRB review research projects involving public benefit programs, we somehow sought to circumvent congressional intent and impose program limits which had been rejected by Congress. More specifically, these comments referred to legislative proposals to permit more extensive use of copayments in the Medicaid program. In fact, any research project involving copayments will not benefit from the exemption since the Secretary has already exercised his discretion to waive application of Part 46 to such projects, pursuant to his authority under 45 CFR 46.101(e). See 47 FR 9208 (March 4, 1982). This provision of the regulations allows the Secretary to waive IRB review for any particular research activity or class of research activity. Thus, the status of co-payments and other similar cost-sharing devices in the Medicaid program will be unaffected by the new exemption. It should also be noted that the recently enacted Tax Equity and Fiscal Responsibility Act includes specific provisions governing demonstration projects involving Medicaid copayments.

9. A few comments asserted that the proposed exemption was contrary to the due process or equal protection clauses of the Constitution because of the possible impact which exempted demonstration projects could have on disadvantaged groups without adequate

opportunity for a hearing. The function of IRB's, however, is not to provide individual claimants with any "due process" right to be heard. At most, IRB's review in a general way broad-based demonstration projects specifically authorized by statute. In our view, an individualized hearing of the sort which typically is associated with "due process" is not appropriate in this context. To the extent that a "hearing" of any sort is called for, the review provided by state and federal program officials is more than adequate to serve that function.

The proposed exemption also raises no issue of equal protection. The only result of the exemption will be that projects involving public benefit programs will not be subject to IRB review while those involving biomedical or behavioral research are. This disparate treatment of different kinds of research activities is, we believe, completely rational and justified in light of the substantially different character of biomedical and behavioral research. Thus, we do not view this different treatment as violative of equal protection.

10. A small number of the comments took issue with the conclusion that Executive Order 12291 was inapplicable to the NPRM. These comments basically argued that the cost to beneficiaries of Medicaid co-payments alone would exceed the Executive Order's threshold figure of $100 million or more in annual effect on the economy. Even if this assertion were accurate, the proposed exemption has no direct effect on projects involving co-payments because they have, as noted above, already been exempted from Part 46 coverage pursuant to the Secretary's waiver authority. Moreover, it is not the IRB review provided by Part 46 which controls the financial impact on Medicaid beneficiaries or other participants in research activity. Instead, program officials—at both the state and federal levels—make the decisions which influence the level of benefits by proposing and approving demonstration projects involving their programs. Thus, the proposed exemption has no direct bearing on any financial impact which may occur as a result of such projects.

Impact Analysis

Economic Impact on Small Entities

The Secretary certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities within the meaning of the Regulatory Flexibility Act, Pub. L. 96–354. Thus, a regulatory flexibility analysis is not required.

Classification of Rule Under E.O. 12291

The Secretary has determined that this rule is not a "major rule" under Executive Order 12291 and thus a regulatory impact analysis is not required. The Secretary's determination is based on the finding that the proposed rule would not:

(1) Have an annual effect on the economy of $100 million or more;

(2) Impose a major increase in costs or prices for consumers, individual industries, federal, state or local government agencies, or geographic regions; or

(3) Result in significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

List of Subjects in 45 CFR Part 46

Civil rights, Government contracts, Grant programs—health, Prisoners, Research, Safety.

Dated: August 26, 1982.

Edward N. Brandt, Jr.,

Assistant Secretary for Health.

Richard S. Schweiker,

Secretary.

PART 46—PROTECTION OF HUMAN SUBJECTS

For the reasons set out in the preamble, Part 46 of 45 CFR is amended as set forth below.

1. Section 46.101 is amended by adding a new paragraph (b)(6) and a new paragraph (i) to read as follows:

§ 46.101 To what do these regulations apply?

* * * * *

(b) * * *

(6) Unless specifically required by statute (and except to the extent specified in paragraph (i)), research and demonstration projects which are conducted by or subject to the approval of the Department of Health and Human Services, and which are designed to study, evaluate, or otherwise examine: (i) Programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

* * * * *

(i) If, following review of proposed research activities that are exempt from these regulations under paragraph (b)(6), the Secretary determines that a research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject of the research or demonstration project, then federal funds may not be expended for such a project without the written, informed consent of each participant or subject.

2. Section 46.116(c) is revised to read as follows:

§ 46.116 General requirements for informed consent.

* * * * *

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

[FR Doc. 83-5549 Filed 3-3-83; 8:45 am]
BILLING CODE 4150-04-M

Correspondence with the Secretary, HHS, on Regulations for Research Involving Children and the Mentally Disabled

F

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

September 16, 1982

Honorable Richard S. Schweiker
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Secretary:

The President's Commission is concerned with how long it is taking the Department of Health and Human Services to issue rules for the protection of children, and of the mentally disabled, in research. I write this letter at the request of the Commission pursuant to our obligation, as stated in Section 1802(c) of the Congressional Act establishing the Commission, to conduct continuing review "of the adequacy...of the rules, policies, guidelines, and regulations of all Federal agencies regarding the protection of human subjects of biomedical and behavioral research."

The Department's liaison has informed us for some time that regulations on research with children were about to be issued, and we now understand that they are in final form, awaiting action in your office. We hope that action will be forthcoming without further delay. Since the draft regulations have not been presented to the Commission for comment, our recommendation that action be taken is not based upon the substance of the regulations or upon a judgment about how well they fulfill the objectives set forth in the recommendations made to the Department in 1977 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Rather, it is our opinion that, pursuant to the relevant Acts of Congress, action is long overdue in moving this field out of its present regulatory limbo.

Your liaison has also informed us that no action is planned in response to the recommendations made in 1978 by the National Commission on research involving institutionalized mental patients, since "no consensus" emerged from the public comments on the proposed regulations published by the Department in November 1978. The President's Commission urges you to act expeditiously to remove regulatory ambiguities and impediments that may exist to research with mentally disabled subjects under conditions that would assure ethical protection to those subjects.

As you will recall, the legislation creating the National Commission (Pub. Law 93-348) required the Secretary of Health, Education and Welfare to publish that Commission's recommendations for comment within 60 days and then to publish the Department's response, in the form of proposed rulemaking, within the 180 days thereafter. Although more than five years have passed since the recommendations on children's research were submitted, and nearly as long since those on the mentally disabled, no action has been taken by your Department.

In light of these delays, the President's Commission, in its First Biennial Report on Protecting Human Subjects, submitted to the President, Congress and heads of affected departments and agencies on December 30, 1981, recommended that prompt action be taken on these topics. This recommendation (Number 5) was made pursuant to §1802(b) of our authorizing legislation, which requires the publication of our recommendations within 60 days (actually accomplished by your Department on behalf of all affected agencies on March 29, 1982) and departmental response within 180 days thereafter.

In making our recommendation, we stated:

> The President's Commission agrees with the National Commission about the importance of pediatric research and of research to prevent or alleviate serious cognitive and emotional disorders. This Commission also shares the concerns of the National Commission that the subjects of such research be properly protected. The Commission concludes, therefore, that the time is long past for action, either by adoption, rejection or modification of the National Commission's recommendations.

We recognize the sensitivity and complexity of these areas of research, as did the Congress in 1974 in asking the National Commission to study these areas. We have also heard repeatedly that the absence of the necessary special provisions for these special research populations creates two problems. On the one hand, such subjects may be inappropriately exposed to risk in projects that do not receive review attuned to the particular problems of such research. On the other hand, some investigators, institutions and Federal funding officials may be unwilling to engage in research in the face of general Federal regulations and state law that they view as unclear and perhaps prohibitory, since no special provisions are made to protect these subjects who cannot give legally effective informed consent for themselves.

Since action on the regulations on children's research seems imminent, our major concern is with the lack of progress on regulations addressing research with the institutionalized mentally disabled. We understand that the National Institute of Aging is attempting to break the log jam in this area by drafting guidelines for research on senile dementia of the Alzheimer's type (a process in which several of our staff have been involved). But from your liaison's testimony at our September 11 hearing, we also understand that no effort is presently under way on the general subject of regulations for research with the mentally disabled. If the Department's 1978 proposed rules have been rejected, we urge you without further delay to convene the relevant people in the Department and to develop rules that take account of valid objections so that important research can proceed with necessary assurances to all involved.

We appreciate your attention to these recommendations and look forward to hearing from you about them.

Sincerely,

Morris B. Abram
Chairman

cc: Assistant Secretary for Health Edward M. Brandt, Jr.
Chairman, Interagency Ad Hoc Committee on
Protection of Human Subjects

Senator Orrin A. Hatch, Chairman
Committee on Labor and Human Resources
Senator Edward M. Kennedy, Ranking Minority Member

Representative Henry A. Waxman, Chairman
Subcommittee on Health and the Environment
of the Committee on Energy and Commerce
Representative Edward R. Madigan
Ranking Minority Member

HARVARD MEDICAL SCHOOL

KENNETH J. RYAN, M.D.
Kate Macy Ladd Professor of
Obstetrics and Gynecology
Chairman of the Department

BRIGHAM AND WOMEN'S HOSPITAL

CHAIRMAN, DEPARTMENT OF
OBSTETRICS AND GYNECOLOGY
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115
Tel: Area Code (617) 732-5444

October 4, 1982

Honorable Richard S. Schweiker
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Secretary:

I write as the former Chairman of the National Commission for the Protection of Human Subjects, to urge that you fulfill your responsibility to issue regulations for research involving the mentally disabled. It has recently been reported that HHS is considering abandoning its efforts to issue such regulations in the foreseeable future. Our Commission, at the request of the U.S. Congress, spent considerable time and effort examining the legal, scientific and ethical issues surrounding such research. We recognized that there was no consensus in the community at large, or even within the scientific community, on appropriate guidelines. However, we were profoundly impressed by the desperate situation in which those who are institutionalized find themselves, and by the urgent need to improve our methods for prevention and care of cognitive and emotional disorders.

It is imperative that important research not be left stranded because of doubts about its ethical acceptability; federal standards would remove many of those doubts. Further, as you are aware, the National Commission was created partly in response to research performed on the mentally retarded that many in our society found morally reprehensible. Such research would still be permissible under current HHS regulations. Nothing in 45 CFR 46 prohibits the enrollment of mentally disabled persons as research subjects against their expressed wishes or in studies totally unrelated to their condition. I cannot believe that you find this acceptable policy for your department.

The U.S. Congress clearly intended that the Commission's recommendations be adopted unless there were cogent reasons, articulated by the Secretary of your Department, not to. I do not believe that a lack of consensus is sufficient justification for modifying the Commission's well-considered recommendations; it certainly cannot justify a decision to decline to issue any regulations whatsoever. Federal regulations would not only protect those human subjects, they would also assist the scientific community by providing guidelines for the ethical conduct of research on the mentally disabled.

R.S. Schweiker
Page Two

I urge you to consider carefully the effect of your actions on the millions of mentally disabled children, adults, and elderly people in this country. For your information, I am attaching a brief summary of the Commission's recommendations in the form of a press release issued in 1978.

Respectfully yours,

Kenneth J. Ryan, M.D., Chairman (1974-1978)
National Commission for the
Protection of Human Subjects of
Biomedical and Behavioral Research

enclosure

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

National Commission Issues Recommendations on Research Involving those Institutionalized as Mentally Infirm

Persons who are institutionalized because of mental illness or retardation will be protected as potential research subjects under recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The Commission's Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm was transmitted on February 8, 1978 to Joseph A. Califano, Secretary of Health, Education, and Welfare (HEW), and to Congress.

The recommendations of the Commission must be taken into consideration in the development of HEW regulations covering any research, conducted or supported by the department, that involves persons who are institutionalized because they are considered mentally infirm. This report is the sixth completed by the Commission since it was established in December 1974.

*Specifically, the Commission recommended that no prospective subject should be approached to participate in research unless a person responsible for the health care of that subject has determined that participation would not interfere with such care; persons who are institutionalized as mentally infirm and who cannot give informed consent should not be involved in research unless it is relevant to their condition; and no one should be involved in research over his or her objection unless the research involves a therapy not otherwise available and the subject's participation is specifically authorized by a court of competent jurisdiction.

*In addition, the Commission recommended that research be approved only after a review board has determined that: the research methods are appropriate to the research objectives; the competence of the investigator and the quality of the research facility are sufficient; if appropriate, studies have been conducted on animals, tissues or cells before involving human subjects; good reasons exist for involving institutionalized persons; any risks of harm or discomfort are minimized; adequate measures are taken to protect the privacy of subjects and confidentiality of data; and selection of subjects is equitable.

The Commission recognized that the term "institutionalized mentally infirm," identified in the original Commission mandate (the National Research Act, Public Law 93-348), includes persons with differing capacities to make decisions regarding participation in research. Also, the level of understanding of individual subjects may fluctuate over a period of time. Therefore, in addition to making provisions for legally valid informed consent, the Commission also provided for accepting a subject's "assent" in order to respect the choices of persons with diminished capacity who are nonetheless able to understand, to make a free choice, and to communicate that choice.

*A subject's assent is sufficient to authorize participation in research which presents no more than minimal risk, so long as the research is relevant to the subject's condition; and for research that holds out the prospect of direct benefit for the individual subject.

*Research that presents more than minimal risk but has no foreseeable benefit to the subjects may involve institutionalized persons only if the risk is a minor increase over minimal; the anticipated knowledge is of vital importance for understanding or alleviating the disorder or the condition of the subject; and the subject does not object. For this category of research, Commission members also determined that the review board should appoint a consent auditor to determine whether the subject consents, assents, or objects to participation in research.

*They also recommended review at the national level by an ethical advisory board for research projects that the local review board believes should be supported because the knowledge to be gained may be of major significance to the solution of a serious health problem affecting persons in mental institutions, but that cannot be approved at the local level under restraints of the previous recommendations.

In the case of review by a national ethical advisory board, provisions should be made for public comment and for Congressional action, if appropriate.

Under provisions of the National Research Act, the Commission's full report was published for public comment in the Federal Register on March 17, 1978. Within 180 days following publication in the Federal Register, the Secretary of HEW must propose regulations to implement the Commission's recommendations or explain any decision not to do so.

# # # # #

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

NOV 5 1982

Mr. Morris B. Abram
Chairman
President's Commission for the Study
of Ethical Problems in Medicine and
Biomedical and Behavioral Research
2000 K Street - Suite 555
Washington, D.C. 20006

Dear Mr. Abram:

I have received your letter of October 7 transmitting your letter and the one of Dr. Ryan to the Secretary concerning regulations for research involving human research subjects institutionalized as mentally disabled. As your letter acknowledges, we are far from achieving consensus in the scientific community or in the Department of Health and Human Services (HHS) concerning appropriate protections for this population. Before we are in a position to issue regulations we need to resolve numerous legal and ethical issues. These include development of better criteria for the determination of competency, qualifications for persons to serve as legally authorized representatives for subjects who are or may become incompetent, and how best to accommodate regulations to the diverse State and local requirements in the area of informed consent.

On September 11, Dr. Charles McCarthy, HHS Liaison to the President's Commission, presented to the Commission some aspects of the lack of consensus in this area. He explained that the National Institute on Aging (NIA) is now diligently working to formulate the basis for guidelines for research with persons with senile dementia of the Alzheimer's type. The NIA staff face extraordinarily complicated issues, however, that are not yet resolved.

The January 1981 regulations for the protection of human subjects require that Institutional Review Boards (IRBs) be especially attentive to additional safeguards to protect the rights and welfare of several categories of subjects likely to be vulnerable to coercion or undue influence, including persons who are afflicted with mental illness. We believe that the IRBs are conscientiously fulfilling this requirement.

We want to act responsibly in applying all regulations for the protection of human research subjects. It would be unwise to promulgate final regulations in this highly controversial and difficult area in view of the degree of divergence of opinion about solutions to ethical and legal

Page 2 - Mr. Morris B. Abram

problems. To do so may jeopardize the well-being of the mentally disabled involved in research and could undermine the integrity of the existing HHS regulations for the protection of human subjects. My discussions within the Department indicate that the absence of regulations setting forth specific protections for subjects institutionalized as mentally disabled is not a deterrent to research in this area; and indeed, research efforts could be impaired if inappropriate regulations were to be promulgated.

Your communication is under consideration by Secretary Schweiker and others in the Department and will contribute to future policy deliberations in this critical area.

Sincerely yours,

E. N. Brandt, Jr.

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

cc: Director, NIH
Acting Director, NIA
Administrator, ADAMHA
Director, NIMH
HHS Liaison to the President's Commission

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

DEC 16 1982

Mr. Morris B. Abram
Chairman
President's Commission for the
Study of Ethical Problems in Medicine and
Biomedical and Behavioral Research
2000 K Street, N.W., Suite 555
Washington, D.C. 20006

Dear Mr. Abram:

This is in response to your letter concerning the development of regulations for the protection of children involved in research and regulations for the protection of persons institutionalized as mentally disabled.

Departmental review of final regulations for the protection of children involved in research is nearing completion. Dr. Charles McCarthy, the HHS liaison to the President's Commission, has apprised the Commission of this.

As you know, in November 1978, the Department published a notice of proposed rulemaking concerning research subjects who are institutionalized as mentally disabled. In addition, the National Institute of Mental Health (NIMH) sought input through meetings with persons representing a wide range of scientific and public perspectives. Members of the staff of the President's Commission attended these sessions and are aware of the lack of consensus concerning the best way to deal with the problems associated with such research subjects. In these meetings and in written comments, many expressed the opinion that additional protections for those institutionalized as mentally disabled could inhibit important research. Others argued that research should not be permitted without additional protections.

In January 1981, the Department published regulations which require Institutional Review Boards to determine that the following requirements are satisfied:

> "Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of the subjects." [46.11(b)]

Page 2 - Mr. Morris B. Abrams

In publishing the notice of proposed rulemaking in 1978 and in publishing the above-quoted provision in January 1981, the Department intended to respond to the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Dr. McCarthy conveyed this information to the President's Commission in testimony on September 11, 1982.

The Department continues to consider specific issues regarding protections for persons institutionalized as mentally disabled, but is not intending to issue additional regulations in the near future. We believe that the current provisions and the review of research by Institutional Review Boards under current regulations provide adequate protections, without undue restraint on research, for persons who are institutionalized as mentally disabled and for other persons whose capacities may be impaired. We are unaware of research that is being delayed or impeded by the absence of additional regulations for subjects who are institutionalized as mentally disabled.

Sincerely,

Richard S. Schweiker
Secretary

Correspondence with the Veterans Administration on Reporting of Research Injuries

G

Department of Medicine and Surgery
Washington D.C. 20420

Veterans Administration

JUL 22 1982

In Reply Refer To: (11M)

Mr. Morris Abram
Chairman
President's Commission for
the Study of Ethical Problems
in Medicine and Biomedical
and Behavioral Research
2000 K Street, N.W.
Suite 555
Washington, D.C. 20006

Dear Mr. Abram:

As you are aware, the Veterans Administration, specifically the Department of Medicine and Surgery's Office of Research and Development, appreciated the dilemma facing the Commission with respect to questions regarding the size of the human subject population and the incidence of adverse results or effects of participation in biomedical and behavioral research. This Agency applauded the Commission's decisions to move forward in these areas in order to amass meaningful data. Previously no reliable data had ever been accumulated to indicate these numbers, beyond mere anecdotal report.

In reliance on the Commission's assurances of intent to recommend that all Federal agencies accumulate specific data in this regard and to define those categories in a fairly meaningful way, the Veterans Administration issued circulars to its medical centers at which research was being carried out, requesting the collection of such data for transmission to Central Office. Preliminary figures were received in November 1981, with early, unreliable, incomplete reports of human subjects "injured" or otherwise adversely affected as the result of their participation in research projects. However, because of definitional problems and apparent misunderstandings by many of our research personnel in the field, and obvious instances of both underreporting and overreporting, the data proved to be unreliable and have been considered meaningless and in some cases misleading. Furthermore, since the data represented so many different frames of reference, they were not amenable to synthesis. These problems were communicated to Commission staff during testimony by Dr. Dorothy Rasinski, our liaison to the Commission, who detailed at length specific problems which the VA had encountered specifically as a result of these "definitional problems". It was anticipated that the Commission would be forthcoming with further guidelines, definitions, specific criteria, etc. to delineate the data it hoped to accumulate, so that the several Federal agencies engaged in or supporting research with human subjects would have more specific guidance in this regard.

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Mr. Morris Abram

The Commission has not issued such guidelines or criteria and, to our understanding, does not plan to do so. Rather, it apparently expects to rely on the VA's experience as a result of trial and error. Of critical significance, no other Federal agencies are at this point collecting such data. Therefore, regardless of how carefully any information may be presented or how extensively the statistics may be asterisked, to call attention to caveats, we are concerned that the VA's experience will of necessity have a negative appearance, with no other data for comparison or serving as a frame of reference. Anecdotal material will be reported as such and may appear "typical", without specific reference to experience in other Federal agencies. Since investigators from different VA medical centers, and even within one center, may be reporting differently in the absence of clarifying guidelines, appropriate comparisons cannot be made. Unwarranted, unjustifiable conclusions based on unreliable data may be drawn and may be extrapolated to an extent that is not at all scientifically valid.

Therefore, in the absence of specific guidelines or definitions, without reporting requirements being uniformly applied to all Federal agencies engaged in the performance or support of research on human subjects, the VA must consider asking its research centers not to gather these data. The current circular requires the reporting of data on November 1, 1982, and, as this date approaches, we anticipate a resumption of the kinds of inquiries requesting clarification that we received last year. Our Research and Development Office will be unable to provide guidance or to draw any meaningful conclusions based on the varieties of information submitted, as these definitions currently stand.

For example, some of our investigators have asked whether the term "human subject" should include every individual whose medical record may be seen and reviewed subsequently, "after the fact," by an epidemiologist. Additionally, should that term apply to every individual whose tissues might be reviewed in retrospect by a pathologist as part of a research project on pathology specimens?

Similarly, the problems of describing or defining adverse results from behavioral or psychological research projects are even more complex. Although our previous communications to the field have requested researchers to report those subjects who were "physically injured" or experienced an unanticipated physical complication as a result of participation in a research project, will the Commission's interest in physical complications as a result of research participation extend only to <u>biomedical</u> research, or will it include physical complications resulting from <u>behavioral</u> or <u>psychological</u> research as well? Further, in those patients

3.

Mr. Morris Abram

who are part of drug research protocols, specifically cancer chemotherapy, there is significant complexity entailed in ascribing "additional hospital days" to the disease process itself (and its natural history) as opposed to a complication of the particular chemotherapeutic agent in use.

We respectfully request your guidance and assistance in this regard, since the task otherwise seems a virtually hopeless one, in our estimation. Our researchers are already being asked to submit large quantities of data to VA Central Office, in addition to various other Federal agencies. To impose an even more restrictive and detailed reporting requirement upon them without giving them the benefit of guidance will not serve to enhance the VA research efforts in support of patient care.

Your comments and guidance in this regard are respectfully requested.

Sincerely,

DONALD L. CUSTIS, M.D.
Chief Medical Director

cc: Dr. Charles R. McCarthy
Director
Office for Protection from
Research Risks

Dr. John A.D. Cooper
Association of American
Medical Colleges

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

August 23, 1982

Donald L. Custis, M.D.
Chief Medical Director
Department of Medicine and Surgery
Veterans Administration
Washington, D.C. 20420

Dear Dr. Custis:

Thank you for your letter of July 22. I am sorry to learn of your agency's difficulties in attempting to implement a requirement for reporting adverse effects of Veterans Administration-sponsored research with human subjects. The VA's willingness to take the lead on this difficult subject is commendable, and I well understand your reluctance to continue, when doing so alone--particularly while methods for producing reliable data are still being perfected--might expose your agency to unjustified criticism.

The Commission still hopes that the VA can assist the other Federal agencies in resolving the definitional problems that you described. As a starting point, in response to the concerns raised in your letter, I would suggest initially limiting your reporting requirements to "bodily injuries" arising in "nontherapeutic" biomedical research or in behavioral research that poses known physical risks. This limitation seems preferable in place of the vague term "adverse effects." In the appendix to its report on Compensating for Research Injuries, the Commission defines "bodily injuries" as

> wounds, infections, disease, temporary or permanent impairments or loss of bodily functions or bodily parts, or death. For reporting purposes, bodily injury does not encompass impairment of mental processes (unless demonstrably associated with a physiological cause or change) or emotional distress.

"Nontherapeutic research" is that which is other than "therapeutic research," which the Commission defines as:

> research to evaluate practices or procedures that are intended to provide, or that have some reasonable possibility of providing, therapeutic, diagnostic or preventive health benefits to subjects.

I believe that this approach would have the following results:

1. Adverse effects of studying experimental therapies ("therapeutic research") would not have to be reported; thus, no problem of distinguishing between the effects of a therapy and the natural course of the underlying disease would arise.

2. Research involving only record reviews or examinations of pathological specimens previously collected for diagnosis or therapeutic purposes would be excluded (because no physical injury could possibly result from such activities).

3. Only physical injuries resulting from behavioral research would be reportable (for example, if a subject received burns from malfunctioning equipment recording eye movements or brain waves).

Possibly, if your staff thought it feasible, adverse effects resulting from "nonbeneficial research procedures" performed as "add-ons" to a therapeutic research program would be reportable. The Commission has suggested the following definition:

> "Nonbeneficial research procedure or intervention" means a research procedure or intervention occurring in either therapeutic or nontherapeutic research that is unnecessary for subjects' own welfare and is performed solely as an aid to the research process.

To be effective, the nontherapeutic procedures whose injuries would be reportable would have to be identified by the IRB in advance; thus, the kind of confusion that could arise in post hoc determinations of adverse effects from experimental therapies should be avoided.

I would be interested in learning your response to these suggestions. I know that Alexander Capron and Barbara Mishkin, the Commission's Director and Deputy, would be pleased to work with you and your staff to refine further these ideas and to review your results thus far. I hope that a satisfactory solution can be found prior to your November deadline. We hope also to have an opportunity to discuss these proposals with members of the AAMC and to benefit from their widsom as well. I understand that the interagency FCCSET group also recognizes that this is an issue requiring further attention in the Federal rules. A cooperative approach to this issue should do much to calm your concern about the VA's lonely position in this regard.

In addition to appreciating the initiative shown by your agency on this issue--to which I hope you will rally other Federal agencies rather than retreating--I want in particular to commend the outstanding job done by your liaison officer, Dr. Dorothy Rasinski. The Commission is on record with its appreciation of Dr. Rasinski's outstanding performance, both during

formal testimony and in responding to requests outside of meetings. Dr. Rasinski did indeed share some concerns in her testimony last November on the VA's initial efforts, but the tone of your letter is much more negative, apparently as a result of your further experience with the data over the past nine months. I hope that some of Dr. Rasinski's optimism that the problems are surmountable can be returned--with greater assurance of its justification.

Sincerely yours

Morris B. Abram
Chairman

cc: Dr. John A.D. Cooper, AAMC
Dr. Charles McCarthy, OPRR

Department of Medicine and Surgery Washington D.C. 20420

Veterans Administration

SEP 14 1982

In Reply Refer To: (11M)

Mr. Morris B. Abram
Chairman
President's Commission for
the Study of Ethical Problems
in Medicine and Biomedical Research
Suite 555
2000 K Street, N.W.
Washington, D.C. 20006

Dear Mr. Abram:

Thank you for your letter of August 23, 1982. The Veterans Administration appreciates your kind comments regarding its attempts to implement a requirement for reporting of adverse effects upon human subject-participants in research activities. The VA has been proud to "lead the way" and show good faith in this very critical area. We would welcome the collaboration of other Federal Agencies involved in or supporting research with human subjects in this effort.

The Veterans Administration certainly appreciates recent efforts of your staff in helping to further define the term "bodily injury" from the standpoint of clarifying the reporting requirement. Similarly, the suggestion that injuries arising in therapeutic research be eliminated, at least for the time being, from such research reporting requirements helps further in solving our dilemmas. Unfortunately, with respect to reporting requirements for Fiscal Year 1982, some investigators who had already gathered data and submitted them to their respective IRB (Human Studies Subcommittee), which group has been collating these data, are no longer active research investigators in the VA. It would be difficult to reexamine and to recapitulate their data now, in the light of a "changed requirement" or definition. Similarly, with researchers who continue active investigation in the VA, there might be resistance to resubmitting, reexamining, and/or reevaluating data which have already been submitted, because of the change in definitions and reporting requirements. Further, IRB staff who have compiled these data would have no way of knowing or discerning how these numbers were gathered since they were required to be submitted anonymously. It would be difficult if not impossible to extract them "after the fact." The data were gathered on the basis of the original definitions provided and cannot now be resynthesized or reevaluated, without difficulty or burden. We had hoped to have received

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Mr. Morris B. Abram

further definitional refinements before this time. To transmit a "definitional change" to our investigators, a definition operational only in the final month, for a year's research experience, would give us a new frame of reference which cannot be retrospectively imposed on already gathered data.

If the Commission can finalize appropriate definitions for reports to be required for projects ongoing during FY 1983 and thereafter, with the data to be submitted to Central Office in November 1983, we will require these definitions and reporting requirements to be transmitted to VA medical centers by October 1, 1982.

As you are already aware, by statute all VA research activities in the Department of Medicine and Surgery are required to be in support of the Agency's quality patient care mission. As a result, the vast majority of VA research projects involving human subjects are perceived as therapeutic in nature. This would significantly decrease the number of "adverse effects" which would be required to be reported, in terms of your suggestion. Adverse responses to therapeutic research activities would be eliminated from reporting requirements. Approximately eighty percent of the investigators in the Veterans Administration are primarily patient health care providers. The remainder are in basic (animal) research activities performed in support of the principal patient care oriented research mission. In addition, the VA by regulation permits no "add-on" or "piggy-back" research.

As you may know, the reporting requirement regarding adverse effects or injuries to research subjects is only one part of a very large data gathering system to which our researchers must provide information annually. Other aspects have been ongoing for a number of years. Continuing this particular reporting requirement at this point may further impair our ability to collect meaningful data in the future. The ongoing credibility of this endeavor may be jeopardized by continuing efforts to collect what appear to be unreliable information.

We trust you can help to clarify this situation for us.

Sincerely,

DONALD L. CUSTIS, M.D.
Chief Medical Director

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

September 24, 1982

Dr. Donald L. Custis
Chief Medical Director
Department of Medicine and Surgery
Veterans Administration
Washington, D.C. 20420

Dear Dr. Custis:

Thank you for your letter of September 14; I am pleased to learn that the VA is still working to develop a useful definition of reportable adverse effect resulting from biomedical research. I am pleased, as well, that the terms suggested in my letter of August 23 seemed an improvement to you.

There appears to be some misunderstanding, however, regarding the framework of my suggestions. The reformulation of reportable injury which I offered was in direct response to your description of the difficulty the VA had experienced with the definition it implemented for FY 1981 reporting requirements. I never meant to suggest that the new definition be applied retroactively to reports already submitted or even to those being readied for FY 1982; rather, I intended to be helpful with any reformulation you might try for reports to be submitted in the future.

The development of an appropriate definition of reportable adverse effect will have to be, as the Commission was fully aware, a process of trial and error. To accomplish necessary adjustments and refinements, and to avoid putting the VA in an isolated position, I hope that the VA will work through the interagency Ad Hoc Committee on Protection of Human Subjects to develop a definition that seems workable, for a start at least, to representatives of all Federal agencies involved in research with human subjects.

D. L. Custis
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Since the Commission has completed its work on the subject of compensation for research injuries, and must complete a number of other reports in the few months remaining before we reach the end of our statutory existence, we are not in a position to provide a more "official" definition. The Ad Hoc Committee, in its role of developing a coordinated Federal response to the Commission's recommendations, would be the appropriate group to assist in further refinement of the definition.

I wish you luck in your labors and thank you, again, for your deligent efforts to be responsive to the Commission's concerns.

Sincerely yours,

Morris B. Abram
Chairman

Sample Evaluation Forms for IRB Site Visitors

H

Inst. IRB Code _____
Reviewer Name _____
Date _____

SITE VISIT COMMENTS
(Please attempt to use the rating scales and provide written comments)

1. Summary overall assessment of IRB.
2. What are the major strengths of this IRB?
3. What are the major weaknesses of this IRB?
4. Is a genuine process of ethical review taking place? (Please comment re the basis of your assessment on this and subsequent questions.)

____ Definitely
____ Probably
____ Mixed evidence
____ Probably not
____ No
____ Unknown

5. How well is the IRB following the regulations and applying sound judgment thereto?

____ Excellent
____ Very well
____ Mixed evidence
____ Not very well
____ Poorly
____ Overprotective
____ Underprotective
____ Unknown

6. Does this IRB give proper weight to protecting subjects' rights and welfare?

____ Definitely
____ Probably
____ Probably not
____ No
____ Unknown

7. Does this IRB place unnecessary or unreasonable obstacles to research?

____ Definitely
____ Probably
____ Probably not
____ No
____ Unknown

8. Does this IRB have adequate support from the institution's administration?

____ Definitely
____ Probably
____ Probably not
____ No
____ Unknown

9. Does this IRB appear to have good acceptance from investigators? Definitely

____ Probably
____ Mixed
____ Probably not
____ No
____ Unknown

10. Does this IRB have clear and adequate authority?

____ Yes
____ No
____ Questionnable
____ Inadequate
____ Unknown

11. How adequate is the range of issues with which this IRB is concerned?

____ Outstanding
____ Adequate
____ Questionnable
____ Inadequate
____ Unknown

12. How adequate is this IRB's composition, in light of amount and types of research reviewed?

____ Outstanding
____ Adequate
____ Questionnable
____ Inadequate
____ Unknown

13. How adequate are its procedures, in light of the amount and types of research reviewed?

____ Outstanding
____ Adequate
____ Questionnable
____ Inadequate
____ Unknown

14. How adequate is its record keeping?

_____ Outstanding
_____ Adequate
_____ Questionnable
_____ Inadequate
_____ Unknown

15. How adequate is its handling of risk/benefit considerations in review?

_____ Outstanding
_____ Adequate
_____ Questionnable
_____ Inadequate
_____ Unknown

16. How adequate is its handling of informed consent issues?

_____ Outstanding
_____ Adequate
_____ Questionnable
_____ Inadequate
_____ Unknown

17. How adequate is its attention to issues of confidentiality and privacy?

_____ Outstanding
_____ Adequate
_____ Questionnable
_____ Inadequate
_____ Unknown

18. How adequate are its policies and practices regarding continuing review?

_____ Outstanding
_____ Adequate
_____ Questionnable
_____ Inadequate
_____ Unknown

19. How adequate are its policies & practices for complaint investigation or other problems that may arise in the conduct of research?

_____ Outstanding
_____ Adequate
_____ Questionnable
_____ Inadequate
_____ Unknown

20. Are there any other aspects of this IRB about which comment is warranted?

Site Visitor _____
Date _____

EVALUATION OF SITE VISIT ITSELF

1. To what extent could you make a firm asserssment of the IRB(s)?

2. To what extent do these site visits seem useful as an educational device?

1. What advance information is needed about institutions to be site visited?

4. How much time should be devoted to site visits, and how should the time be allocated?

5. How important is it to meet with IRB members? How useful are individual versus group meetings with IRB members?

6. How important is it to meet with investigations? How should they be selected? Should these meetings be individual?

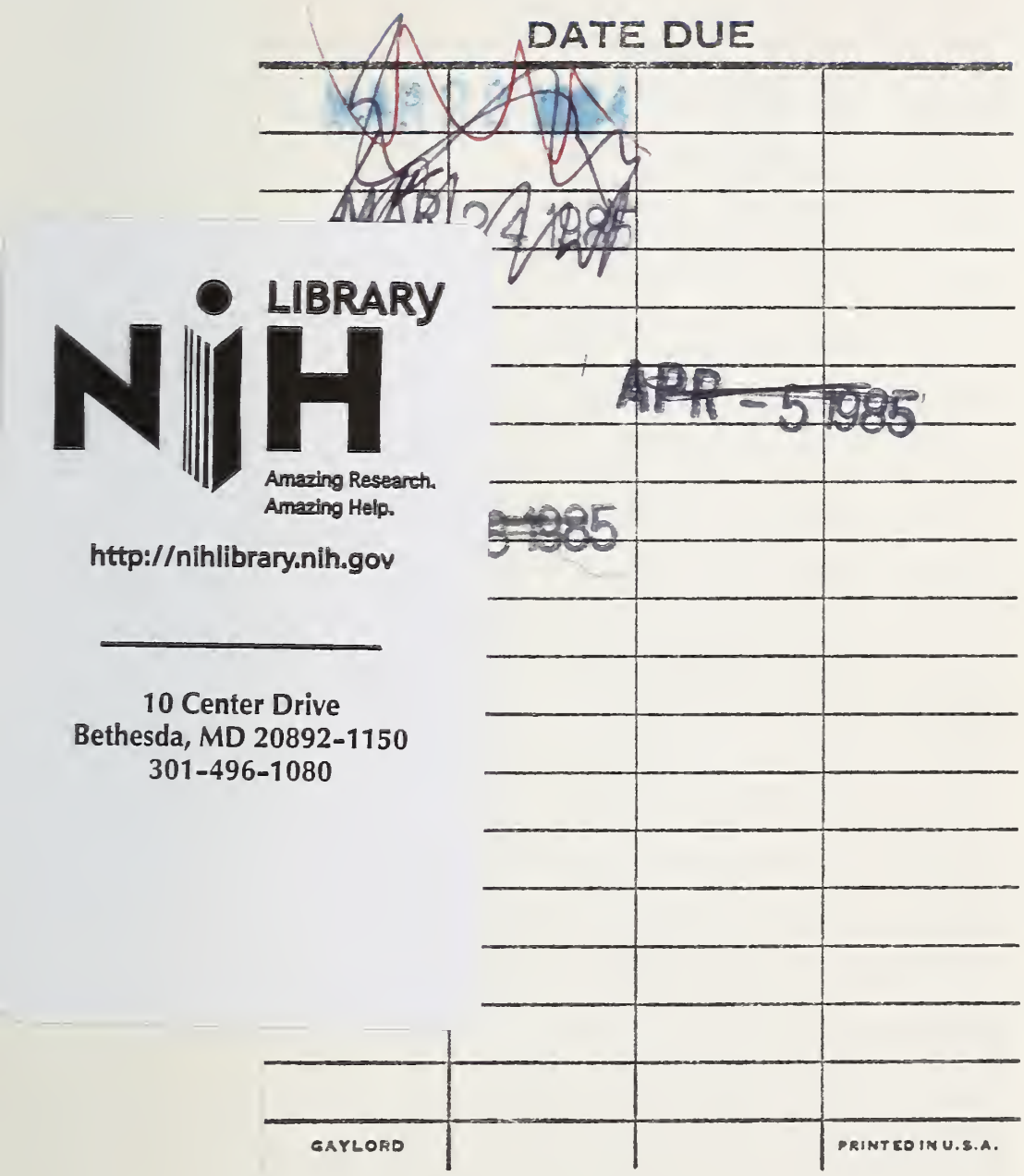
7. How important is it to attend an IRB meeting? Is it uniquely useful in any ways?

8. How useful is it (or would it be) to attempt to reconstruct the review of particular proposals (with records, IRB members, and the investigator)?

9. Have you any suggestions regarding numbers and types of site visitors?

10. Other comments and suggestions regarding these site visits?

New Book 12-19-83



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